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POLYPHARMACY IN CANCER PATIENTS: HEALTH-RELATED QUALITY OF LIFE, EXPENDITURES, AND ADVERSE EVENTS

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POLYPHARMACY IN CANCER PATIENTS: HEALTH-RELATED QUALITY OF LIFE, EXPENDITURES, AND ADVERSE EVENTS

BY

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Abstract

Polypharmacy (PP), often defined as the use of five or more medications, is highly prevalent in patients with cancer. As the quantity of medications for treating cancer and comorbid conditions in patients with cancer become more numerous and diverse, it is important to understand the various ways in which patient health and economic outcomes may be adversely affected by prescribed medications. The purpose of this dissertation was to investigate three distinct associations between PP and the lives of patients living with cancer by estimating how PP (1) affects health-related quality of life (HRQoL), (2) is associated with healthcare expenditures, and (3) affects health complications (HCs).

Approximately 25% of cancer survivors, individuals who were diagnosed with cancer and are still alive, report a decreased quality of life related to physical problems, and 10% report a decreased quality of life related to emotional issues, compared to their noncancer counterparts (10% and 6%, respectively). Specifically, cancer survivors report more mobility issues, inferior health, higher psychological distress, and more mental health needs. There is scant published literature describing PP in contributing to these outcomes. This study was conducted to address this gap to better inform cancer survivors, care providers, and health policy decision makers.

Cancer was the sixth most expensive condition to treat in the United States (US) in 2015. Most cancers are estimated to have a decreasing incidence and

increasing survival rate for the foreseeable future. A decreasing incidence may cause overall cancer-related expenditures to decline over time, but the prevalence of cancer coupled with the aging of the US population will result in an increase in the number of cancer survivors. Thus, expenditures during treatment through end of life are expected to continue to increase in coming years, as cancer survivors are estimated to increase from 15.5 million in 2016, to 26.1 million by 2040.

Common cancer-related ailments such as pain, emesis, depression, venous thrombosis, and seizures can require prescription medications. With additional medications arises the risk for a health complication (HC). A HC, for the purposes of this study, is defined as an adverse health problem related to a drug, including adverse drug reactions, worsening of disease symptoms, falls, or overdoses. Although many HCs are preventable, they represent approximately 125,000 hospitalizations, over 3.5 million physician office visits, and an estimated 1 million emergency department visits each year in the general population. Previously identified risk factors for HCs in people with cancer, depending on the type of cancer, include PP, advanced stage of cancer, higher comorbidity, gender (for colorectal cancer), older age, and prior ER visits or hospitalizations.

The purpose of the studies in this dissertation was to advance understanding of the role of PP on health and economic outcomes among people with cancer. We examined two data sources: (1) a large national survey database for manuscripts 1 and

2, and (2) a large, commercial claims database of privately-insured individuals for manuscript 3; both of which included United States (US) populations.

Manuscript 1: The intent of this manuscript was to evaluate if an association exists between PP and HRQoL in cancer survivors in the US. The analysis used self-reported answers to questions about various demographic and clinical information captured in the Medical Expenditures Panel Survey (MEPS) database for even years 2008-2014. Respondents, who stated they were told that they had cancer, answered questions from the SF-12v2 about their physical and mental health, which were converted to the HRQoL measures PCS and MCS used for this analysis. This study focused on comparing cancer survivors, defined as having ≥ 5 prescribed medication classes in the year of the interview, with those with less than 5 medication classes. Differences among types of cancer were also explored in both descriptive and regression analyses. This study hypothesized that PP would lead to lower HRQoL as compared to patients not having PP. Of 10.1 million survivors per year included in this study, 45% were defined as having PP. We used ordinary least squares (OLS) regression to estimate that PP was associated with a statistically and clinically significant decrease in PCS scores among cancer survivors by 3.75 points. However, PP was not associated with a significant decrease in MCS scores. As such, PP should be analyzed closely in cancer survivors to ensure the best possible HRQoL.

Manuscript 2: Healthcare expenditures are increasing in the US, and that is especially true for patients living with cancer. The objective of this manuscript was to

determine if PP was associated with increased direct health care expenditures, and if differences in expenditure exist according to cancer type or setting of care. This aim was accomplished by using the same years and source of data as Manuscript 1, while modeling expenditure as a dependent variable. We hypothesized that PP was associated with increased health expenditures in total, by type of cancer and by setting of care. We used OLS regression with log transformed expenditures to obtain estimates of association between PP and increased health expenditures controlling for various demographic, socioeconomic, and clinical variables. PP was present in 43.9% of the 10.6 million (per year) cancer survivors in the study. PP was associated with a mean annual adjusted healthcare expenditure per cancer survivor of $13,266 (SD $3,766), which was significantly higher than those without PP $8,573 (SD 5,082, p-value <.0001). Cancer survivors with PP accounted for 70% of total healthcare expenditures, yet only comprised 43.9% of the population.

Manuscript 3: This study focused on newly diagnosed patients with breast, prostate, colorectal, or lung cancer and investigated if an association exists between PP and nonfatal health complications (HCs). The data source used was Optum Clinformatics® DataMart (Optum, Eden Prairie, MN, USA), years 2010-2015. The database contains de-identified claims information with medical, prescription drug, enrollment, and other data tables. PP was measured as the use of ≥ 5 prescribed medication classes in the quarter (3 months) following incident cancer diagnosis. HCs was the dependent variable in the analysis and included a range of medical conditions known to be caused or worsened by effects of medications including falls, fractures,

gastrointestinal bleeding, and delirium. Descriptive and logistic regression analyses were conducted to assess any associations between PP and HCs in a multivariable framework. This study hypothesized that HCs would occur more frequently among patients with PP than those without PP. In the primary analysis using multivariable LR modeling, PP was associated with 31% increased odds (adjusted odds ratio: aOR) of having ≥ 1 HCs, controlling for age, region, type of cancer, comorbidities, radiation and chemotherapy treatments. PP was significantly associated with a higher risk of having ≥ 1 HC in each cancer type (aOR: breast 1.37, 95% CI: 1.31-1.42; prostate 1.27, CI: 1.22-1.32; colorectal 1.26, CI: 1.16-1.36; lung 1.25, CI: 1.11-1.40). Active chemotherapy was associated with significantly increased odds of ≥ 1 HC in colorectal (aOR: 1.35, CI: 1.21-1.50) and lung (aOR: 1.33, CI: 1.15-1.54) cancers, but not significantly associated with breast or prostate cancers. Newly diagnosed patients with breast, prostate, colorectal, or lung cancer were all at a higher risk of having ≥ 1 HCs if defined as having PP compared to those without PP. Active chemotherapy treatment was associated with increased risk of HCs in colorectal and lung cancer patients, but not in breast or prostate cancer patients.

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I would also like to thank my co-major committee member Dr. Ami Vyas for her diligence in reviewing my work and providing helpful suggestions on topics I did not know much about prior to this dissertation. She helped guide me through the research process and always responded promptly whenever I had a question. Without her assistance, I would not have been able to complete this research. For these things, I will always be grateful.

In addition to my co-major committee members, I would also like to thank the other members of my committee, Dr. Aisling Caffrey and Dr. Mary Greaney, for their contributions in shaping this dissertation. Dr. Caffrey was also my mentor and leader of my multi-year appointment as the database manager for our Health Outcomes group within the College of Pharmacy. I learned a great deal in that time, especially how to manipulate data and think more methodologically. Dr. Greaney helped shape my dissertation with her years of experience as a researcher in health studies. Her

suggestions helped me focus on the importance of both methods and the ability to relay information to researchers in disciplines other than health outcomes.

I would be remiss if I did not mention my friends and previous graduates of the program: Dr. Hilary Aroke, Dr. Ajinkya Pawar, and Dr.Yizhou Ye. Many times, during this program and dissertation process, I felt overwhelmed by the sheer scope of what lay before me. These individuals were always willing to speak, text, and email with me to answer any questions. They have my sincerest gratitude.

Lastly, I would like to acknowledge both the support provided and sacrifices made by my family and significant other during my time in the program at the University of Rhode Island. I simply could not have accomplished this without them.

Preface

The manuscript format was used to examine three distinct associations between polypharmacy (PP), often defined as the use of multiple medications, and the lives of patients living with cancer by estimating how PP (1) affects health-related quality of life (HRQoL), (2) is associated with healthcare expenditures, and (3) affects health complications (HCs). I hope this work is impactful.

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MANUSCRIPT 1

Title: Association between polypharmacy and health-related quality of life among cancer survivors in the United States.

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1.1 Abstract

PURPOSE: Polypharmacy (PP) is present in many cancer survivors and may lead to lowered health-related quality of life (HRQoL). The objective of this study was to evaluate the association between PP and HRQoL among non-institutionalized cancer survivors living in the United States (US).

METHODS: A cross-sectional analysis of Medical Expenditure Panel Survey (MEPS), a set of surveys of households, their medical providers and employers throughout the US was conducted. Our analytic sample included all adult patients with a clinical classification code for cancer, during even years 2008-2014. PP was defined as reported use of five or more therapeutic classes of prescription medications. The MEPS measured HRQoL using the Short Form 12-Item Health Survey Version 2 (SF-12v2) Physical Component Summary (PCS) and Mental Component Summary (MCS) scores. Ordinary least squares regression was used to assess associations between PP and HRQoL controlling for various demographic, socioeconomic, and clinical factors.

RESULTS: An estimated 10.1 million cancer survivors per calendar year were analyzed in this study. Cancer survivors were mostly white (81.8%), female (56.0%), and under the age of 65 (51.6%). Female breast (17.2%), prostate (13.7%), and melanoma (7.3%) were the most prevalent cancer types. PP was present among 44.4% of cancer survivors. After adjusting for covariates, the mean PCS score for survivors with PP was 35.8 points, which was significantly lower compared to those without PP (39.5) by 3.7 points (p-value <.0001). Conversely, PP was not significantly associated with differences in the mean MCS score compared to survivors without PP (44.9 vs.

45.4, respectively) in multivariable regression analyses adjusting for demographic, socioeconomic, and clinical variables.

CONCLUSIONS: Cancer survivors with PP accounted for approximately 45% of the analyzed sample and had a significantly lower PCS score than their counterparts without PP.

IMPLICATIONS FOR CANCER SURVIVORS: PP should be examined closely by cancer survivors because of increased associations with poorer physical domain of quality of life.

1.2 Introduction

Approximately 25% of cancer survivors, individuals who were diagnosed with cancer and are still alive, report a decreased quality of life related to physical problems and 10% report a decreased quality of life related to emotional issues compared to their noncancer counterparts (10% and 6%, respectively).[1] Specifically, cancer survivors report more mobility issues, inferior health, higher psychological distress, and more mental health needs.[1] They also worry about recurrence of their malignancy, new types of neoplasms,[2] and the possible long-term damage their cancer treatment may cause.[3] These concerns are additional to normal apprehensions about aging and the occurrence of comorbidities.[4] Approximately 70% of cancer survivors have one or more comorbidities.[5] Many observational studies have reported that cancer patients have poorer survival if they have comorbidities.[6]

Cancer has a systemic impact on both body and mind.[1] Treating these impacts usually leads to greater use of prescription medications.[7,8] Cancer patients may have underlying comorbid conditions prior to their cancer diagnosis requiring medication therapy. As the number of medications increases with medication therapy for cancer, concurrent multiple medications treating both comorbid conditions and cancer may lead to polypharmacy (PP). A cross-sectional study using the Medical Expenditure Panel Survey (MEPS) database, estimated the prevalence of PP, defined by the study as ≥ 5 unique prescription medications, to be 64% among cancer survivors, compared to 51.5% in the non-cancer control group.[5] The study found that the median number of

unique prescription medications was 6 for cancer survivors, but only 4 for noncancer controls, despite the majority (55%) of survivors having been diagnosed ≥ 5 years previously.[5]

As cancer survivors receive an increased number of concomitant medications, they become at an increased risk of dangerous adverse event occurrence.[9] Concerns about PP arise from certain harmful situations, such as when unforeseen or unintended drug effects and drug-drug interactions result in health complications.[10] Short-term, long-term, and late effects of cancer treatments,[11] related, in-part, to prescribed chemotherapy regimens may also negatively impact cancer survivors.[12] Treatment effects include a wide variety of impacts to organs, tissues, body development, growth, mood, feelings, actions, thinking, learning, memory, social and psychological adjustment, and risk of second cancers.[12] Treating these late effects to alleviate discomfort can require additional medications such as analgesics for pain,[13] and corticosteroids to help breathe normally,[14] among other drugs for symptoms which may decrease health-related quality of life (HRQoL).[1]

A retrospective cohort study of adults (21 years and older) with arthritis conducted using the MEPS, found that PP was associated with significantly lower physical HRQoL scores.[15] Based on this evidence and the negative impacts of cancer on HRQoL, investigating the relationship between PP and HRQoL in the cancer survivor population was warranted. The objective of this study was to evaluate this

association between PP and HRQoL among cancer survivors living in the US using a nationally representative survey database.

1.3 Methods

Study design and data source

We used a multi-year cross-sectional study design to analyze the MEPS, a publicly available database which contains survey questionnaire responses of de-identified non-institutionalized persons and their families (households), their medical providers, and employers in the US.[16] The MEPS includes five interviews over the course of 2 calendar years conducted via computer assisted personal interviewing (CAPI). The multiple interviews allow for (1) analyzing how people's healthcare changes over time and (2) minimizing recall bias.[17] The MEPS also permits weighting of the data to produce nationally representative estimates of the US population for various healthcare analyses (e.g. expenditures, utilization of resources, insurance plans).[16]

Two major components are included in the MEPS: household and insurance.[16] We selected the longitudinal, medical conditions, and prescribed medicines files from the household component for this study and linked them through a unique identifier for each individual.[16] We first used the medical conditions file to find individuals who reported having been diagnosed with cancer by using the cancer specific clinical classification codes; which are defined using the Clinical Classification Software provided by the Agency for Healthcare Research and Quality (AHRQ) which clusters diagnoses codes into a manageable number of categories.[18] Respondents were defined as cancer survivors during the interview process if they answered affirmatively to the

question “Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?” Those who confirmed having, or had, cancer were asked what type of cancer and their age at diagnosis.[19] We also used clinical classification codes and the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes to identify concurrent chronic conditions. Further details regarding MEPS have been described elsewhere.[16]

Sample selection

We combined the MEPS data for years 2008, 2010, 2012, and 2014 for our analyses. In the MEPS process of interviewing, individuals are followed for two years, therefore we selected even years to avoid including repeated observations. Respondents with cancer other than nonmelanoma skin cancer, who were at least 18 years of age at the time of response, were included in this study. We excluded those who had missing, negative, or zero person-level sample weights. To limit the effect of multiple cancers on the estimated relationship between PP and HRQoL, individuals were excluded if they had more than one type of cancer.[19] We also excluded those who died during the calendar year due to possible inflated prescription counts during end-of-life care and the possible effect terminal cancer would have on HRQoL scores. In one retrospective cross-sectional study of 4,252 hospice patients across 11 states in the US, 35% of whom had cancer, the mean number of prescriptions was 15.[20] Figure 1 shows a flowchart of inclusion and exclusion criteria.

Measures

Dependent variable

Health-related quality of life

We chose the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores, calculated from the Medical Outcomes Study Short-Form 12 Health Survey Version 2 (SF-12v2) as our dependent variables. The SF-12v2 is collected as part of the MEPS during rounds 2 and 4 of the survey to measure HRQoL.[21] Included in the survey for PCS are questions which focus on the general health, mobility activity, limitations on activities or work, vitality, and pain.[21] The MCS has questions regarding whether depression and anxiety have an impact on accomplishments or work, mental health regarding feelings of calm and peacefulness, and social activities limitations.[21] PCS and MCS scores range from 0 to 100 and are calibrated so that 50 is the mean score with a standard deviation of 10 for the general US population.[22] For both PCS and MCS scores, a higher score indicates a better HRQoL. The SF-12v2 has been proven as both reliable and valid for measuring HRQoL in the cancer survivor population using the MEPS.[23]

Key independent variable

Polypharmacy

A consensus definition of PP does not currently exist.[24] Some investigators have measured PP by individual drug or classes of medications.[15,24]

The MEPS provides a prescriptions file with therapeutic medication class information which are linked to the Multum Lexicon database for analysis.[25] We used these therapeutic class details to determine the maximum number of classes of prescription medications the individuals were prescribed in one of the rounds that coincided with our study years. We defined PP as using ≥ 5 therapeutic classes of medications in one of the rounds of interviews, which is consistent with other definitions in published literature.[15,26]

Covariates

Demographic variables included age group based on quartile analysis, sex, race/ethnicity, geographic region, and marital status.

Socioeconomic variables included income, insurance status, and level of education. A person's income level was categorized as low, middle, or high; where low indicates a person is below 200% above the poverty line, middle indicates 200% to 400% above the poverty line, and high indicates 400% or greater income than the poverty line. Insurance was categorized as privately-insured, uninsured, or publicly-insured. Level of education was classified into 3 groups: less than high school (i.e. did not graduate), high school graduate, and some college (must not have graduated to be included).

Clinical variables included type of cancer, time since cancer diagnosis, select chronic conditions common in cancer survivors, and number of total healthcare

encounters. We classified cancer into several groups based on logical groupings or sample size (if a specific type of cancer had too small a count to be its own subclass). The cancer type groups were the following: breast, prostate and other male genitals (included testicular cancer), cervical and other female genitals (included uterine, ovarian, other female cancers), colon and other gastrointestinal (GI) (stomach, liver, pancreas, and other GI cancers), melanoma, leukemias/lymphomas, and other or unspecified (included lung) (Appendix A). We created a variable for time (years) since cancer diagnosis by subtracting the person's reported age at diagnosis from their reported age at the time of the survey because it was found to be a significant indicator of HRQoL among certain cancer groups.[19] For patients who could not remember, or otherwise did not provide a response for age at diagnosis, we used a statistical multiple imputation procedure to assign time since cancer diagnosis.[27] Multiple imputation is an iterative process which uses the distribution of the observed data to estimate the true value of the missing variable. Values produced were used in regression analysis with the results pooled through statistical software to make valid inferences about the parameters and standard errors. To fit the structure of the variable, we used a minimum value of 0 (years) and maximum value of 85 (years). We achieved a relative efficiency of 99.0% and 99.1% with 25 imputations for our PCS and MCS models, respectively.[28] Comorbidities were selected from a list of priority health physical conditions provided by the MEPS and included the following: arthritis, chronic obstructive pulmonary disease, diabetes, and heart disease/cardiovascular ailments.[26] We chose these comorbidities based on MEPS' recognition that they are more prevalent, expensive, or especially relevant to healthcare policy as well as their impact

on physical functioning.[29] To assess the influence of mental health conditions in our study population, we selected mood disorders (bipolar and depression) and anxiety disorders, using the MEPS designated mental health disorders clinical classification codes to identify these conditions for each patient (Appendix B). We dichotomized these conditions as either present (1) or absent (0). Healthcare encounters were defined as total provider or outpatient visits obtained from the household files and categorized based on quartiles into the following groups: 0-4, 5-9, 10-19, and ≥ 20 visits.

Statistical analysis

We used chi-square tests to determine the statistical significance of differences in presence or absence of PP for each independent variable (IV) according to statistical significance (p-value <0.05). Analysis of variance (ANOVA) was used to assess the relationship between the various levels of the categorical variables with the dependent variables (DVs), where p-values <0.05 indicated a significant relationship. To estimate the mean scores for PCS between those with or without PP, T tests were used controlling for significant covariates. Mean PCS and MCS score differences by PP with 95% confidence intervals were calculated as part of the T tests.

Univariate OLS regression models were used to test the significance of association for each covariate by using the magnitude of the F value and p-value statistic; whereby, significance of p-value < 0.10 resulted in the variable being included in the multivariable OLS regression modeling process. If the variable was significantly associated with both PP and PCS/MCS then they were held for further

analysis in the modeling process. To ensure the IVs were not correlated with one another the variance inflation factor (VIF), variance decomposition proportions (VDFs), and condition indices (CNIs) options provided in the SAS procedural software were used. If covariates had a VIF of ≥ 5.0, VDFs ≥ 0.5 (for two variables), or CNI ≥ 30, collinearity would have been assumed and removal of one of the IVs would have occurred.[30] However, neither the PCS nor MCS models' variables reached these thresholds.

Multivariable OLS regression was used to evaluate the association between PP and PCS/MCS scores controlling for all significant covariates. The ability to predict physical or mental well-being by a covariate was judged by its p-value significance level (p-value ≤ 0.05) in the multivariable modeling process. In the model building process, covariates were included sequentially based on p-value and F-value significance. If two covariates had the same p-value (e.g. <.0001), then the covariate with the largest F-value was considered more significantly associated with the DV. The adjusted model's overall fit was measured using the coefficient of multiple determination adjusted R^2. When adding covariates to the model no longer produced a better fitting model (higher adjusted R^2 = better fit), a manual stepwise process was implemented. This process involved removing a covariate which was significant in univariate analysis, with a high F-value, but when added to the multivariable model became insignificant. This stepwise technique was used until only significant covariates were left. Parameter (beta, β) estimates with standard errors (SE) were used to determine the direction and magnitude of association between PP and PCS/MCS

scores. Parameter direction and magnitude were evaluated at each iteration of the model building process to verify no multicollinearity existed, which would have been evidenced by a large change in magnitude or direction, and/or a large jump in adjusted R^2 despite a variable not being significantly associated with the DV.

Due to the complexity of the survey design used in the MEPS; stratification, clustering, and weighting were performed to control for clustering and unequal probability design.[31] Significance tests were all performed at the $\alpha = 0.05$ level. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

1.4 Results

The study population consisted of an unweighted total of 3,281 adult cancer survivors (Table 1). This sample represented approximately 10.1 million non-institutionalized cancer survivors per calendar year living in the US. Weighted percentages per annum for the 3 most prevalent specified types of cancer in the study were breast (17.2%), prostate (13.7%), and melanoma (7.3%) with the largest single group being other/unspecified (44.8%). Table 2 includes the proportions of all independent variables in total by PP or no PP. The sex of the cancer survivors was the only variable without significant difference between groups for those with or without PP (p=0.4899). Older survivors (≥75) had PP in greater proportion (60.9%) than younger survivors (18-49: 18.5%). Survivors of cervical cancer had the lowest percentage of PP (38.1%); while survivors of leukemias and lymphomas had the highest (50.1%). Approximately 60% or more of the survivors with PP also had chronic conditions (arthritis 59.7%; COPD 69.7%; heart conditions 63.8%; diabetes 77.6%; anxiety 66.3%; mood 67.3%) which was significantly different than those without PP (p-value <.0001). Of the cancer survivors included in this study, 1,460 (weighted N=4,471,359; 44.4%) reported use of ≥ 5 therapeutic classes of prescribed medications. Table 3 highlights that the 10 most frequently reported therapeutic classes of prescribed medications were very similar for those with PP and those without. Between those with PP and those without PP, only 6 therapeutic classes differed in total. In the PP group, the patients reported to be prescribed diuretics, antidiabetic agents, and anticonvulsants more frequently compared to dermatological

agents, antihypertensive combinations, and macrolide derivatives in the without PP groups. The 10 most commonly prescribed therapeutic classes for those with PP made up 42.8%, whereas those without PP was 48.3% of the total number of prescribed therapies.

Adjusted mean PCS and MCS with mean differences by PP

Significantly lower mean PCS scores existed for all survivors with PP except those with prostate cancer (Figure 2). Survivors of cervical and other female genital cancers with PP had the lowest mean PCS score difference of 6.8 points [95% CI: 2.4-11.3], or 17.9%, compared to women without PP (31.1 [26.4-35.7] versus 37.9 [33.4-42.5], p-value 0.0027). Colon and other GI cancers had a similarly low mean PCS score difference of 6.7 points [2.7-10.6], or 15.6%, in those with PP compared to those without PP (35.8 [31.4-40.3] versus 42.5 [38.2-46.8], p-value 0.0012). Adjusted mean MCS score differences by PP were not statistically significant for any individual type of cancer. Adjusted mean PCS and MCS, as well as mean difference significance by cancer type, with or without PP are depicted in Figure 2.

Associations between PP and PCS/MCS scores

Mean adjusted PCS scores for those with PP (35.76 [95% Confidence Interval: 34.30-37.23]) were significantly associated (p-value <.0001) with lower PCS scores by 3.75 [2.63-4.87] points compared to those without PP (39.51 [37.97-41.06]) when controlling for all variables associated with both PP and MCS/PCS in the model

(Table 4). No type of cancer was significantly different from their referent group of leukemias and lymphomas for the PCS multivariable OLS model.

Table 4 provides the findings from the unadjusted and adjusted OLS regression models to determine the significance of association between PP and PCS, controlling for all investigated variables which had at least one group significantly different from their referent group. Patients who were aged ≥ 75 had mean PCS scores which were significantly lower than the youngest age group (18-34 years) by more than 3 points (β= -3.35 SE 0.71 p-value <.0001) when controlling for all other significant variables in the model. Survivors with arthritis (β= -4.76 SE 0.50 p-value <.0001), COPD (β= -4.36 SE 0.67 p-value <.0001), diabetes (β= -2.83 SE 0.62 p-value <.0001), and heart conditions (β= -2.05 SE 0.53 p-value= 0.0001) had PCS scores significantly lower compared to survivors without those comorbid conditions. Individuals with ≥ 20 healthcare encounters had PCS scores nearly 4 points lower than those with < 5 encounters (β= -3.71 SE 0.62 p-value <.0001).

In the multivariable regression model for MCS, mean MCS scores for those with PP (44.90 [43.6-46.2]) were not significantly different than survivors without PP (45.41 [44.1-46.8]), having a mean difference of 0.51 points lower ([0.49-1.51], p-value= 0.3145), when controlling for all significant variables (Table 5). When controlling for significant variables in the OLS model, colon or other type of GI cancer was the only type of cancer significantly associated with MCS scores. The scores for those with colon or other type of GI cancer were approximately 2.5 points

lower than patients with leukemia or lymphoma (β= -2.34 SE 1.13 p-value= 0.0381). This 2.5-point difference represents a clinically meaningful difference in physical health from leukemia or lymphoma. Arthritis (β= -1.78 SE 0.41 p-value <.0001), anxiety (β= -2.98 SE 0.67 p-value <.0001), and mood disorders (β= -8.08 SE 0.67 p-value <.0001) were associated with significantly lower MCS scores in adjusted analysis. Individuals with the lowest level of income had significantly lower MCS scores compared to those with the highest income by over 3 points (β= -3.25 SE 0.53 p-value <.0001). Advanced age was associated with better MCS scores (50-64: β= 1.35 SE 0.58 p-value= 0.0196; 65-74: β= 3.93 SE 0.69 p-value= <.0001; and ≥ 75: β= 3.86 SE 0.71 p-value <.0001) compared to those 18-49 years old. Gender, race, marital status, region, education, number of healthcare encounters, COPD, diabetes, heart conditions, and time since cancer diagnosis were not significantly associated with MCS.

1.5 Discussion

Our study contributes to the literature by being the only research, to the authors' knowledge, examining the association between PP and HRQoL among adult cancer survivors in the US using nationally representative survey data. The study findings suggest that PP is associated with lower PCS scores by approximately 4 points among adult cancer survivors in the US. We were not surprised by these results since management of chronic conditions among cancer survivors often requires multiple prescription medications including nonsteroidal anti-inflammatory drugs, benzodiazepines, antidepressants, and opioids, which often affect major organ systems.[5]

Polypharmacy

We found that nearly half (44.4%) of cancer survivors were prescribed ≥ 5 distinct therapeutic classes of medications, thus were classified as having PP according to our definition. We consider this to be a conservative estimate of the true number of medications a patient was taking, as we did not count individual medications, for which patients could be using multiple medications from the same therapeutic class. In a systematic review of definitions for PP, 80.4% of 138 articles had a numerical value for the definition, 10.9% had numerical along with duration of therapy or healthcare setting, and 8.7% had descriptive definitions.[24] The outcome of the systematic review was that the most commonly used definition for PP was ≥ 5 daily prescription medications (46.4% of 110 articles meeting final inclusion

criteria).[24] In a recently published survey study of 385 cancer survivors aged 70 or older, where the researchers were evaluating ranges of PP cut-points to a range of adverse events (falls, frailty) determined that using ≥ 5 medications concomitantly is reasonable for identifying at-risk patients.[32] Murphy et al. examined individual medication counts among cancer survivors using the MEPS and found that approximately 64% of cancer survivors were taking ≥ 5 distinct medications concomitantly and had more physical limitation in adults 18 years and older.[5] However, their study did not look at mental health conditions or PCS/MCS as outcomes.

High pill burden has been associated with increased use of inappropriate medication, thus increasing the risk of adverse outcomes.[33] In a medical chart review of 244 cancer patients aged ≥70 years receiving chemotherapy, 39% of severe potential drug interactions involved chemotherapeutic agents.[34] Additionally, the authors found that cancer patients' risk of a potential drug interaction increases with each additional medication, up to 100% when 8 or more medications were being taken concomitantly.[34] These risk estimates are higher than those reported in noncancer populations.[34] However, not all PP can be considered inappropriate, as multiple medication use does occur commonly in cancer survivors and may be the result of appropriately treating multiple conditions. A closer look at the root causes should be undertaken to try to eliminate excessive risks of inappropriate PP, such as lack of integrated and coordinated care, and possible contraindicated drug-drug interactions, which may lead to adverse events.[35] Conversely, not addressing adverse situations

requiring medications in a timely manner may lead to avoidable complications. However, this study was not intended to address appropriateness of prescribed medications and requires further investigation in the future.

PCS

Minimum clinically significant differences using the SF-12v2 range from 2-5 points from the population mean of 50.[36,37] The difference in the adjusted analysis was 3.75 points, which met the lower bound of minimum clinically significant threshold. This difference of 3.75 points represents the change in mean score of PCS with a one-unit change in PP (or a person switching from no PP to PP). Meaning that for someone in the general population with a PCS score of 50 and without PP, reaching the PP threshold of ≥ 5 unique classes of prescribed medications would be associated with having a worse PCS score by 3.75 points and be a proxy for worse physical domain of HRQoL.

We did not find any published study which evaluated the association between PP and HRQoL in cancer survivors; however, a study had reported that cancer survivors were more likely to have physical limitations (29.0% vs. 21.6%), and worse overall health status than their noncancer counterparts (29.7% vs. 18.4%, respectively).[5] In this study, we found PP was associated with worse PCS scores, after adjusting for comorbidity and age, among other covariates. As PCS is derived from questions about both general health and physical specific, it is possible that PP

decreases only specific areas covered by the PCS summary score. However, individual items were not analyzed in this analysis.

MCS

PP was not significantly associated with changes in MCS scores in cancer survivors compared to those without PP in our multivariable analyses, regarding statistical or clinically meaningful differences. Colorectal cancer was the only type of cancer which had a statistically and clinically meaningful difference in reported mental and emotional health by more than 2 points compared to patients with leukemia or lymphoma. According to LeMasters et al., who conducted a retrospective cross-sectional analysis using the Behavioral Risk Factor Surveillance System (BRFSS) survey, female colorectal cancer survivors have a significantly increased number of days as perceived bad mental health in the past month compared to matched noncancer controls.[38] In a US population-based study, no difference was found in quality of life scores between women with cervical cancer versus those without.[39] In our study, cervical cancer was not significantly associated with poorer PCS or MCS scores compared to leukemias and lymphomas.

Previous research has shown significant associations among the covariates included in this study, which was our basis for including them. For example, Weaver et al., using the 2010 National Health Interview Survey, found that among 1,822 adult cancer survivors who responded to the PROMIS Global 10, a 10-item patient-reported outcomes survey, lower education and > 1 comorbidity were independently associated

with poor physical HRQoL.[1] Also, among their findings and consistent with ours is that lower socioeconomic status was associated with poorer physical and mental health. Weaver et al. also found that younger age was associated with poorer mental health. Lastly, the Weaver et al. study found no differences among races/ethnicities for either physical or mental health and measurements of quality of life, a finding similar to what we found in multivariable analysis.[1] In a study by Wang et al. conducted using the MEPS data, of 3,610 cancer survivors, the prevalence of each cancer type was similar to this study where 20.1% had breast, 15.0% had prostate, and 8.4% had melanoma.[19]

PP in cancer survivors has been a concern for many years and this study confirms that use of multiple medications is still highly prevalent and warrants further attention in all cancer survivors. More consideration should be paid to continuity of care for cancer survivors to ensure appropriate medication use and non-medication management for chronic conditions. The study findings support the need for future research aimed at identifying the classes of prescription medications and the clinically significant drug-drug interactions that may cause survivors to report decreased physical QoL measured by PCS scores. Therefore, healthcare providers should evaluate the benefits and harms of prescribing multiple medications for cancer survivors.

1.6 Limitations

Some limitations exist due to the nature of the data source. As the MEPS has a survey design depending on a person's ability to remember various life events, responses are subject to recall bias. Also, the MEPS does not capture information on stage or severity of cancer which affects both PP and HRQoL, and so we could not adjust for these variables in our analyses. PP was not assessed for association with responses to specific mental or physical health states from the SF12-v2 since we used the summarized scoring totals for PCS and MCS; therefore, we cannot allude to any specific physical or mental functioning that may have been impacted by PP. Despite controlling for various comorbidities, severity of those illnesses could not be captured. We cannot make assumptions as to a causal effect that the cancer treatment, or the cancer itself, may have had on specific chronic conditions.

As we evaluated the association between PP and HRQoL among cancer survivors by therapeutic class, some information may have been lost due to multiple drugs being used within the same class. Also, because this was cross-sectional, we cannot determine if an individual's PCS or MCS scores changed over time with the addition or subtraction of medications. As PP is a proxy for measure of disease burden, it is likely that survivors were appropriately taking multiple medications to help address comorbid conditions rather than their comorbid conditions were due to taking so many medications. However, this paper's intent was not to address appropriate versus inappropriate PP, hence further research is needed to better

understand PP's impact on HRQoL. Though the association between cancer and PP has been reported previously,[5] to our knowledge, no study had evaluated how PP is associated with HRQoL among adult cancer survivors in the US.

1.7 Conclusion

In this cross-sectional study of community-dwelling cancer survivors in the US, PP was associated with lower PCS scores in certain types of cancer and those with higher comorbidity burden. Cancer survivors, their support system, providers, and all other pertinent stakeholders should have a vested interest in understanding how PP impacts the survivors' lives to maximize HRQoL. PP should be examined closely by cancer survivors because of possible increased associations with poorer physical domain of quality of life.

1.8 References

1. Weaver KE, Forsythe LP, Reeve BB, et al. Mental and physical health-related quality of life among U.S. cancer survivors: population estimates from the 2010 National Health Interview Survey. Cancer Epidemiol Biomarkers Prev. 2012 Nov;21(11):2108-17. doi 10.1158/1055-9965.EPI-12-0740. Epub 2012 Oct 30. PubMed PMID: 23112268; PubMed Central PMCID: PMC3645867.

2. Cancer Treatment & Survivorship Facts & Figures 2016-2017 is accompanied by "Cancer Treatment and Survivorship Statistics, 2016," a scientific paper published in the American Cancer Society Journal, CA: A Cancer Journal for Clinicians.

3. Koch L, Jansen L, Brenner H, Arndt V. Fear of recurrence and disease progression in long-term (≥ 5 years) cancer survivors – a systematic review of quantitative studies. Psychooncology. 2013 Jan;22(1): 1-11. doi 10.1002/pon.3022. Epub 2012 Jan 10. Review. PubMed PMID: 22232030.

4. Rowland JH, Bellizzi KM. Cancer Survivorship Issues: Life after treatment and implications for an aging population. J Clin Oncol 2014 Aug 20;32(24):2662-8. doi: 10.1200/JCO.2014.55.8361. Epub 2014 Jul 28. Review. PubMed PMID: 25071099; PubMed Central PMCID: PMC4164810.

5. Murphy CC, Fulling HM, Alvarez CA, et al. Polypharmacy and patterns of prescription medication use among cancer survivors. Cancer. 2018 Jul 1;124(13). doi 10.1002/cncr.31389. Epub 2018 Apr 12. PubMed PMID: 29645083; PubMed Central PMCID: PMC6147245.

6. Søgaard M, Thomsen RW, Bossen KS, et al. The impact of comorbidity on cancer survival: a review. Clin Epidemiol. 2013 Nov 1; 5(Suppl 1): 3–29. doi: 10.2147/CLEP.S47150. Review. PubMed PMID: 24227920; PubMed Central PMCID: PMC3820483.

7. Loh KY, Ng T, Lee CP, Ng R, Chan A. Medication use by early-stage breast cancer survivors: a 1-year longitudinal study. Support Care Cancer. 2016 Apr;24(4):1639-47. doi: 10.1007/s00520-015-2950-z. Epub 2015 Sep 25. PubMed PMID: 26404861; PubMed Central PMCID: PMC4766201.

8. Maggiore RJ, Gross CP, Hurria A. Polypharmacy in older adults with cancer. Oncologist. 2010;15(5):507–522. doi: 10.1634/theoncologist.2009-0290. Epub 2010 Apr 24. Review. PubMed PMID: 20418534; PubMed Central PMCID: PMC3227983.

9. van Leeuwen RWF, Brundel DHS, Neef C, et al. Prevalence of potential drug-drug interactions in cancer patients treated with oral anticancer drugs. Br J Cancer 2013 Mar 19;108(5):1071-8. doi 10.1038/bjc.2013.48. Epub 2013 Feb 14. PubMed PMID: 23412102; PubMed Central PMCID: PMC3619066.

10. van Leeuwen RWF, Jansman FGA, van den Bemt, et al. Drug-drug interactions in patients treated for cancer: a prospective study on clinical interventions. Ann Oncol. 2015 May;26(5):992-7. doi: 10.1093/annonc/mdv029. Epub 2015 Jan 26. PubMed PMID: 25628444.

11. Aziz NM. Cancer survivorship research: state of knowledge, challenges and opportunities. Acta Oncol. 2007;46(4):417–432. Review. PubMed PMID: 17497308.

12. National Cancer Institute (NCI). Late effects of treatment for childhood cancer (PDQ®)–patient version was originally published by the National Cancer Institute. Available Online: https://www.cancer.gov/types/childhood-cancers/late-effects-pdq. Accessed March 1, 2018.

13. Lu R, Krull KR, Leisenring W, et al. Pain in long-term adult survivors of childhood cancers and their siblings: A report from the Childhood Cancer Survivor Study. Pain. 2011 November;152(11): 2616–24. doi 10.1016/j.pain.2011.08.006. Epub 2011 Sep 9. PubMed PMID: 21907493; PubMed Central PMCID: PMC3304496.

14. Limper AH. Chemotherapy-induced lung disease. Clin Chest Med. 2004 Mar;25(1):53-64. Review. PMID:15062597. doi:10.1016/S0272-5231(03)00123-0.

15. Meraya AM, Dwibedi N, Sambamoorthi U. Polypharmacy and Health-Related Quality of Life Among US Adults With Arthritis, Medical Expenditure Panel Survey, 2010-2012. Prev Chronic Dis. 2016 Sep 22;13:E132. doi: 10.5888/pcd13.160092. PubMed PMID: 27657504; PubMed Central PMCID: PMC5034554.

16. Medical Expenditure Panel Survey; Agency for Healthcare Research and Quality. Available: https://meps.ahrq.gov/mepsweb/. Accessed February 16, 2018.

17. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey, HC-138: 2010 Full Year Consolidated Data File; 2012. https://meps.ahrq.gov/data_stats/download_data/pufs/h138/h138doc.pdf. Accessed November 7, 2018.

18. Machlin S, Soni A, Fang Z. Understanding and analyzing MEPS Household Component Medical Condition Data. Available Online: https://meps.ahrq.gov/survey_comp/MEPS_condition_data.shtml. Accessed November 7, 2018.

19. Wang SY, Hsu SH, Gross CP, Sanft T, Davidoff AJ, Ma X, Yu JB. Association between Time since Cancer Diagnosis and Health-Related Quality of Life: A Population-Level Analysis. Value Health. 2016 Jul-Aug;19(5):631-8. doi: 10.1016/j.jval.2016.02.010. Epub 2016 Apr 7. PubMed PMID: 27565280; PubMed Central PMCID: PMC5002308.

20. Sera L, McPherson ML, Holmes HM. Commonly prescribed medications in a population of hospice patients. Am J Hosp Palliat Care. 2014 Mar;31(2):126-31. doi: 10.1177/1049909113476132. Epub 2013 Feb 12. PubMed PMID: 23408370; PubMed Central PMCID: PMC3830696.

21. Cheak-Zamora NC, Wyrwich KW, McBride TD. Reliability and validity of the SF12-v2 in the medical expenditure panel survey. Qual Life Res. 2009 Aug;18(6):727-35. doi: 10.1007/s11136-009-9483-1. Epub 2009 May 8. PubMed PMID: 19424821.

22. Park J, Look KA. Relationship Between Objective Financial Burden and the Health-Related Quality of Life and Mental Health of Patients With Cancer. J Oncol Pract. 2018 Feb;14(2):e113-e121. doi: 10.1200/JOP.2017.027136. Epub 2018 Jan 30. PubMed PMID: 29381411.

23. Bhandari NR, Kathe N, Hayes C, Payakachat N. Reliability and validity of SF-12v2 among adults with self-reported cancer. Res Social Adm Pharm. 2018 Nov;14(11):1080-1084. doi: 10.1016/j.sapharm.2018.01.007. Epub 2018 Jan 31. PubMed PMID: 29366669.

24. Masnoon N, Shakib S, Kalisch-Ellett L, Caughry GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017 Oct 10;17(1):230. doi: 10.1186/s12877-017-0621-2. Review. PubMed PMID: 29017448; PubMed Central PMCID: PMC5635569.

25. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey, HC-135A: 2010 Prescribed Medicines; 2012. https://meps.ahrq.gov/data_stats/download_data/pufs/h135a/h135adoc.pdf. Accessed November 7, 2018.

26. Vyas A, Babcock Z, Kogut S. Impact of depression treatment on health-related quality of life among adults with cancer and depression: a population-level analysis. J Cancer Surviv. 2017 Oct;11(5):624-633. doi: 10.1007/s11764-017-0635-y. Epub 2017 Aug 10. PubMed PMID: 28799098.

27. Yuan Y. Multiple Imputation Using SAS Software. J Stat Software. 2011;45(6). ISSN: 1548-7660 (Online).

28. Smith C, Kosten S. Multiple Imputation: a statistical programming story. PharmaSUG 2017 – Paper SP01. Available Online: https://pharmasug.org/proceedings/2017/SP/PharmaSUG-2017-SP01.pdf. Accessed September 13, 2018.

29. MEPS Topics: Medical conditions file. Medical Expenditure Panel Survey; Agency for Healthcare Research and Quality. Available: https://meps.ahrq.gov/mepsweb/data_stats/MEPS_topics.jsp?topicid=32Z-1. Accessed February 17, 2018.

30. Kleinbaum DG, Klein M. Logistic Regression: A Self-Learning Text. 3rd Ed. New York: Springer, 2010.

31. Vyas A, Pan X, Sambamoorthi U. Chronic Condition Clusters and Polypharmacy among Adults. Int J Family Med. 2012;2012:193168. doi: 10.1155/2012/193168. Epub 2012 Aug 1. PubMed PMID: 22900173; PubMed Central PMCID: PMC3415173.

32. Turner JP, Jamsen KS, Shakib S, Singhal N, Prowse R, Bell JS. Polypharmacy cut-points in older people with cancer: how many medications are too many? Support Care Cancer. 2016 Apr;24(4):1831-40. doi: 10.1007/s00520-015-2970-8. Epub 2015 Oct 9. PubMed PMID: 26449548.

33. Sharma M, Loh KP, Nightingale G, Mohile SG, Holmes HM. Polypharmacy and potentially inappropriate medication use in geriatric oncology. J Geriatr Oncol. 2016 Sep;7(5): 346–53. doi: 10.1016/j.jgo.2016.07.010. Epub 2016 Aug 3. Review. PubMed PMID: 27498305; PubMed Central PMCID: PMC5037024.

34. Popa MA, Wallace KJ, Brunello A, Extermann M, Balducci L. Potential drug interactions and chemotoxicity in older patients with cancer receiving chemotherapy. J Geriatr Oncol. 2014 Jul;5(3):307-14. doi: 10.1016/j.jgo.2014.04.002. Epub 2014 May 10. PubMed PMID: 24821377; PubMed Central PMCID: PMC4154059.

35. Lees J, Chan A. Polypharmacy in elderly patients with cancer: clinical implications and management. Lancet Oncol. 2011 Dec;12(13):1249-57. doi: 10.1016/S1470-2045(11)70040-7. Epub 2011 Jul 6. Review. PubMed PMID: 21741307.

36. Cheung AS, de Rooy C, Hoermann R, Joon DL, Zajac JD, Grossmann M. Quality of life decrements in men with prostate cancer undergoing androgen deprivation therapy. Clin Endocrinol (Oxf). 2017 Mar;86(3):388-394. doi: 10.1111/cen.13249. Epub 2016 Nov 2. PubMed PMID: 27696495.

37. Roydhouse JK, Gutman R, Keating NL, Mor V, Wilson IB. Proxy and patient reports of health-related quality of life in a national cancer survey. Health Qual Life Outcomes 2018 Jan 5;16(1):6. doi: 10.1186/s12955-017-0823-5. PubMed PMID: 29304818; PubMed Central PMCID: PMC5756370.

38. LeMasters T, Madhavan S, Sambamoorthi U, Kurian S. A population-based study comparing HRQoL among breast, prostate, and colorectal cancer survivors to propensity score matched controls, by cancer type, and gender. Psychooncology. 2013 Oct;22(10):2270-82. doi: 10.1002/pon.3288. Epub 2013 Apr 19. PubMed PMID: 23606210; PubMed Central PMCID: PMC4892175.

39. Greenwald HP, McCorkle R, Baumgartner K, Gotay Carolyn, Neale AV. Quality of life and disparities among long-term cervical cancer survivors. J Cancer Surviv (2014) 8:419–426. doi 10.1007/s11764-014-0352-8.

Figure 1. Selection of Patients for Analyses of Prevalence of Polypharmacy in Adult Cancer Survivors (≥ 18 years) (2008, 2010, 2012, 2014), unweighted.

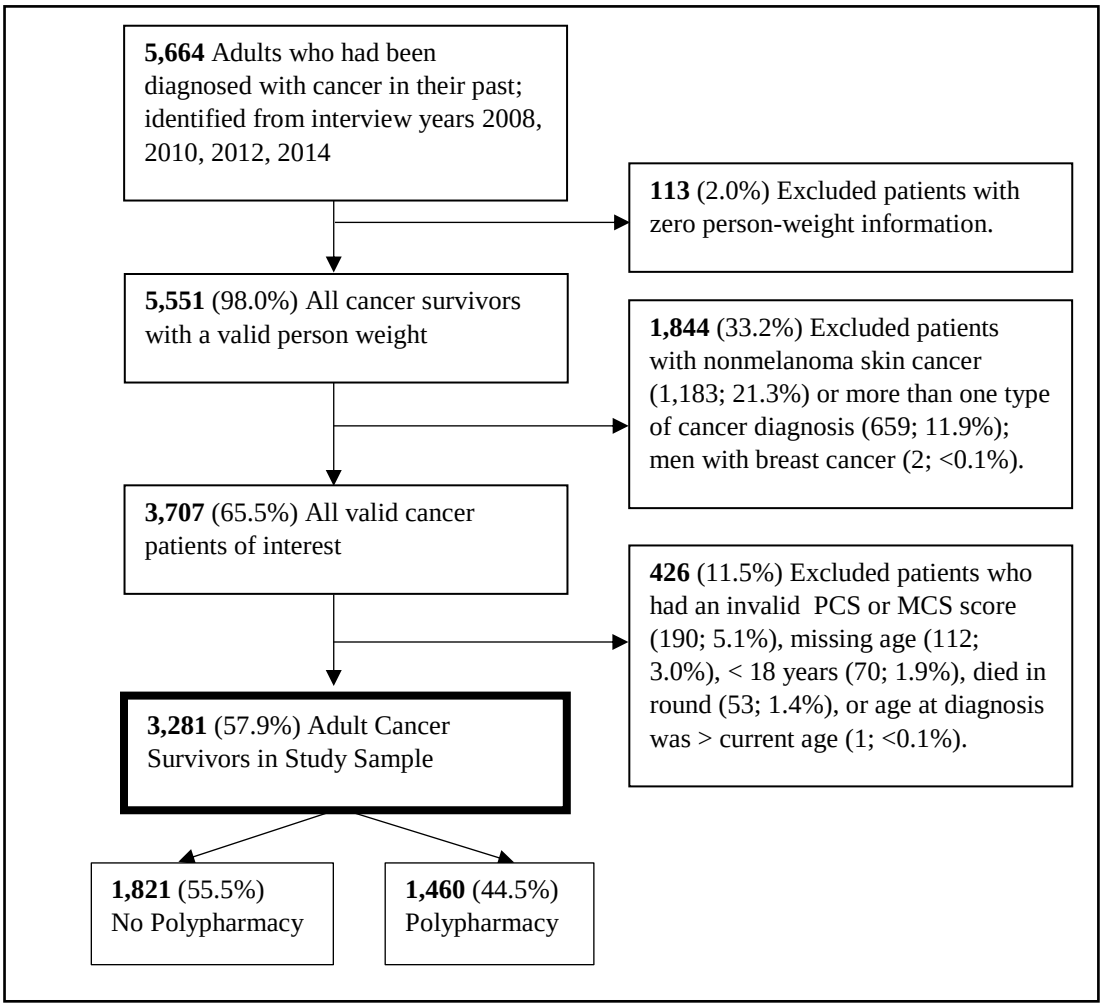


Table 1. Distribution of Cancer Diagnoses in Adult Cancer Survivors (≥ 18 years) (2008, 2010, 2012, 2014) of Interest Available in MEPS.

Type of Cancer	N (%), weighted
Breast	1,730,969 (17.2%)
Prostate and other male genital	1,382,904 (13.7%)
Cervical and other female genital	594,733 (5.9%)
Colon and other GI	644,921 (6.4%)
Melanoma	731,028 (7.3%)
Leukemias and lymphomas	467,401 (4.6%)
Other / unspecified	4,524,103 (44.9%)
Total	**10,076,059 (100.0%)**

Table 2. Demographic and Clinical Characteristics of Adult (≥ 18 years) Cancer Survivors (N= 10,076,059) with Cancer Diagnoses of Interest 2008, 2010, 2012, 2014, Weighted n (%).

Demographic and Clinical Characteristics	No Polypharmacy	Polypharmacy	p-value[e]
Total	n= 5,604,700 (55.6%)	n= 4,471,359 (44.4%)	
Age group (years)[a]			<.0001
18-49	1,667,385 (81.5)	377,514 (18.5)	
50-64	1,881,319 (59.6)	1,277,488 (40.4)	
65-74	1,161,289 (44.9)	1,425,711 (55.1)	
≥ 75	894,707 (39.1)	1,390,646 (60.9)	
Sex			0.4899
Men	2,430,618 (54.8)	2,002,535 (45.2)	
Women	3,174,081 (56.2)	2,468,825 (43.8)	
Race			0.0143
White	4,552,749 (55.3)	3,685,943 (44.7)	
African American	399,601 (50.4)	393,249 (49.6)	
Hispanic	402,539 (63.5)	231,205 (36.5)	
Other	249,810 (60.8)	160,962 (39.2)	
Region			0.007
Northeast	1,192,725 (57.9)	866,216 (42.1)	
Midwest	1,161,836 (52.6)	1,047,874 (47.4)	
South	1,876,790 (52.1)	1,723,153 (47.9)	
West	1,373,348 (62.2)	834,117 (37.8)	
Type of Cancer[b]			0.0415
Breast	905,173 (52.3)	825,795 (47.7)	
Prostate/other male genital	700,133 (50.6)	682,770 (49.4)	
Cervical/other female genital	367,847 (61.9)	226,886 (38.1)	
Colon/other gastrointestinal	331,340 (51.4)	313,581 (48.6)	
Melanoma	445,029 (60.9)	285,999 (39.1)	
Leukemias and Lymphomas	233,040 (49.9)	234,362 (50.1)	
Other/unspecified	2,622,137 (58.0)	1,901,966 (42.0)	
Healthcare Encounters			<.0001
≤ 4	1,763,347 (81.9)	389,527 (18.1)	
5 - 9	1,671,371 (64.3)	927,650 (35.7)	
10 - 19	1,352,039 (47.8)	1,475,045 (52.2)	
≥ 20	817,943 (32.8)	1,679,137 (67.2)	
Marital Status			0.0062
Married	3,554,793 (57.9)	2,584,969 (42.1)	
Not Married	2,049,907 (52.1)	1,886,390 (47.9)	
Education Level			<.0001
Less than High School	2,524,157 (52.7)	2,261,309 (47.3)	
High School	909,690 (50.2)	901,685 (49.8)	
Some College	2,170,853 (62.4)	1,308,365 (37.6)	
Income Level[c]			<.0001
Low	1,327,712 (46.5)	1,525,131 (53.5)	
Medium	1,472,878 (55.1)	1,201,854 (44.9)	
High	2,804,110 (61.7)	1,744,374 (38.3)	
Insurance Coverage			<.0001
Private	4,175,600 (59.5)	2,840,116 (40.5)	
Uninsured	316,594 (84.9)	56,407 (15.1)	
Public	1,112,506 (41.4)	1,574,836 (58.6)	
Time since cancer diagnosis (years)			0.0005

≤ 2	1,013,155 (58.2)	727,923 (41.8)	
3 - 5	1,023,246 (57.1)	767,357 (42.9)	
6 - 10	1,826,313 (58.3)	1,305,332 (41.7)	
> 10	1,741,987 (51.0)	1,670,750 (49.0)	
Arthritis[d]			<.0001
Yes	1,806,317 (40.3)	2,670,963 (59.7)	
COPD[d]			<.0001
Yes	537,824 (30.3)	1,235,408 (69.7)	
Diabetes[d]			<.0001
Yes	442,667 (22.4)	1,531,746 (77.6)	
Heart conditions[d]			<.0001
Yes	2,112,035 (36.2)	3,717,153 (63.8)	
Anxiety disorders[d]			<.0001
Yes	517,393 (33.7)	1,019,466 (66.3)	
Mood (depression + bipolar)[d]			<.0001
Yes	555,323 (32.7)	1,140,712 (67.3)	

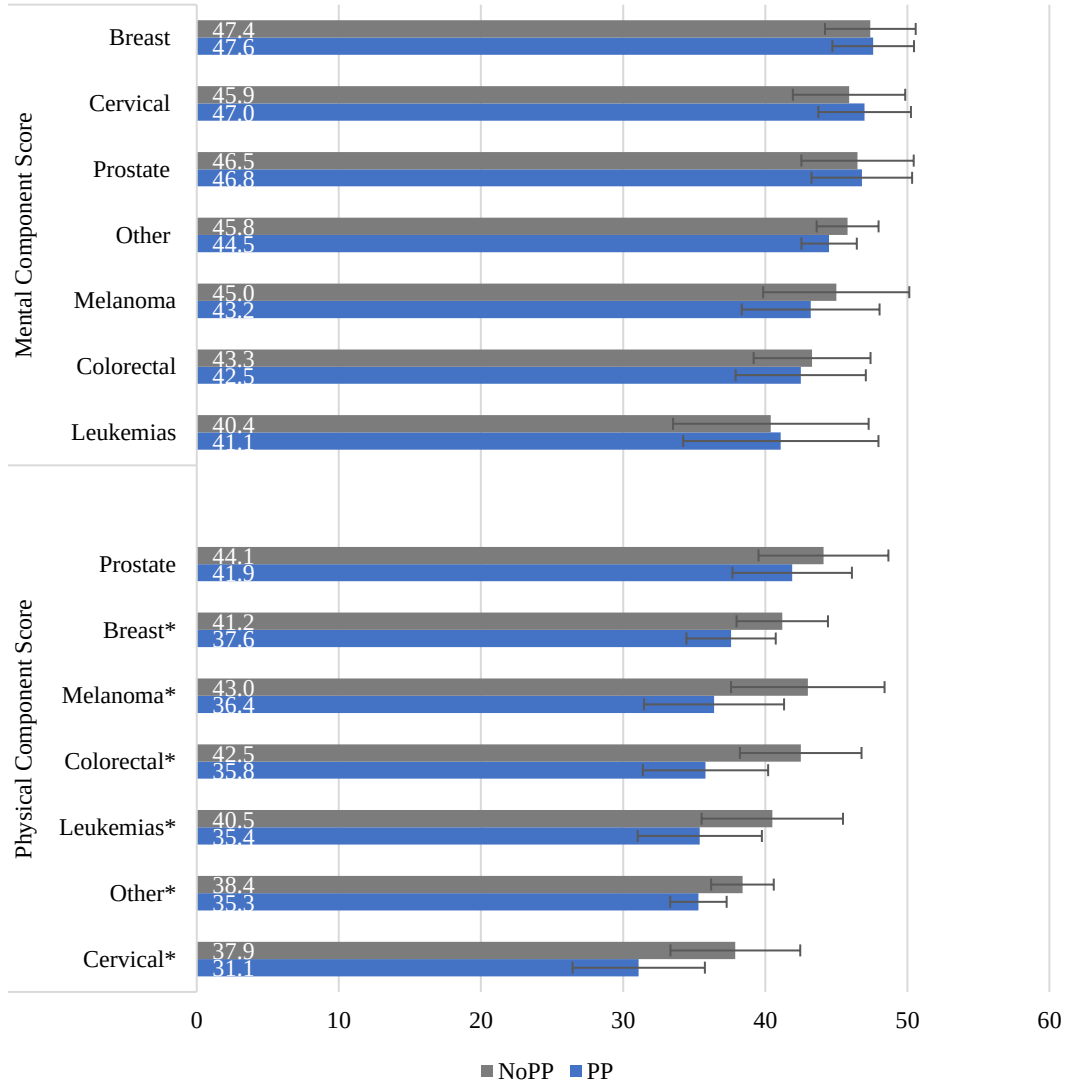
Notes: [a]The Medical Expenditures Panel Survey sets an upper limit of 85 years old.
[b]Type of cancer included the following categorizations: prostate (included testicular cancer and cancer of other male genitals), cervical (included uterine, ovarian, other female cancers), colorectal (esophageal, stomach, colon, rectum and anus, liver and intrahepatic bile duct, pancreas, and other gastrointestinal cancers).
[c]Income level: low (<200% above poverty line), medium (200% to 400% above poverty line), high (>400% above the poverty line).
[d]Arthritis, chronic obstructive pulmonary disease (COPD), diabetes, heart conditions, anxiety and mood disorders are binary values (No=not present, Yes=present) listed in Appendix B.
[e]Chi-square statistics were used to assess significant differences.

Table 3. The 10 Most Frequently Prescribed Therapeutic Classes by Polypharmacy in US Adult (≥ 18 years) Cancer Survivors for 2008, 2010, 2012, 2014 (N=10,076,059), weighted n %.

No Polypharmacy			Polypharmacy		
Therapeutic Class	**n**	**%**	**Therapeutic Class**	**n**	**%**
Analgesics	5,641,955	9.8	Antihyperlipidemic Agents	10,756,303	7.0
Antihyperlipidemic Agents	5,271,895	9.1	Analgesics	10,026,041	6.5
Thyroid Hormones	2,594,923	4.5	Beta-Adrenergic Blocking Agents	6,880,568	4.5
Antidepressants	2,568,521	4.4	ACEIs	6,191,953	4.0
Beta-Adrenergic Blocking Agents	2,162,874	3.7	Antidepressants	6,059,182	3.9
ACEIs	2,011,395	3.5	Proton Pump Inhibitors	6,008,914	3.9
Dermatologic Agents	2,002,805	3.5	Diuretics	5,734,144	3.7
Proton Pump Inhibitors	1,961,436	3.4	Antidiabetic Agents	5,501,999	3.6
Macrolide Derivatives	1,875,861	3.2	Anticonvulsants	4,701,619	3.0
Antihypertensive Combinations	1,811,742	3.1	Thyroid Hormones	4,348,843	2.8

Notes: ACEIs = Angiotensin Converting Enzyme Inhibitors.

Figure 2. Adjusted Mental and Physical Component Scores by Cancer Type, with or without Polypharmacy, Means with 95% Confidence Interval Bars (N =10,076,059).



* = statistically significant mean differences between mean scores at alpha = 0.05. NoPP = No polypharmacy. PP = polypharmacy.

Type of cancer included the following categorizations: prostate (included testicular cancer and cancer of other male genitals), cervical (included uterine, ovarian, other female cancers), colorectal (esophageal, stomach, colon, rectum and anus, liver and intrahepatic bile duct, pancreas, and other gastrointestinal cancers).

Table 4. Unadjusted and Adjusted Regression Estimates (Beta) with Standard Errors (SE) of Significant Explanatory Variables Based on an Ordinary Least Squares Regression Model for Patient and Clinical Factors Associated with Physical Component Scores (PCS) in US Adult Cancer Survivors (≥ 18 years) for 2008, 2010, 2012, 2014 (N=10,076,059).

Explanatory Variables	*Unadjusted Model*		*Adjusted Model*	
	Beta (SE)	**P value**	**Beta (SE)**	**P value**
Polypharmacy				
Yes	-10.23 (0.51)	<.0001	-3.75 (0.57)	**<.0001**
Age Group, years				
18-49	***Reference***			
50-64	-3.83 (0.69)	<.0001	-1.29 (0.58)	**0.0277**
65-74	-6.19 (0.72)	<.0001	-0.92 (0.65)	0.1600
≥ 75	-9.99 (0.69)	<.0001	-3.35 (0.71)	**<.0001**
Region				
Northeast	***Reference***			
Midwest	-2.22 (0.83)	0.0085	-1.28 (0.76)	0.0951
South	-2.69 (0.71)	0.0002	-1.84 (0.65)	**0.0050**
West	0.23 (0.77)	0.7610	0.24 (0.67)	0.7216
Education Level				
Less than High School	-4.28 (0.53)	<.0001	-1.16 (0.44)	**0.0097**
High School	-5.84 (0.78)	<.0001	-2.98 (0.64)	**<.0001**
Some College	***Reference***			
Income Level[a]				
Low	-7.80 (0.64)	<.0001	-3.65 (0.63)	**<.0001**
Medium	-3.51 (0.61)	<.0001	-1.58 (0.53)	**0.0034**
High	***Reference***			
Insurance Coverage				
Private	***Reference***			
Public	-7.16 (0.60)	<.0001	-2.56 (0.56)	**<.0001**
Uninsured	-0.82 (1.30)	0.5289	-2.27 (1.16)	0.0518
Arthritis[b]				
Yes	-8.72 (0.47)	<.0001	-4.76 (0.50)	**<.0001**
COPD[b]				
Yes	-8.62 (0.73)	<.0001	-4.36 (0.67)	**<.0001**
Heart Conditions[b]				
Yes	-8.01 (0.52)	<.0001	-2.83 (0.62)	**<.0001**
Diabetes[b]				
Yes	-7.50 (0.66)	<.0001	-2.05 (0.53)	**<.0001**
Healthcare Encounters (no. of visits)				
0 - 4	***Reference***			
5 - 9	-1.32 (0.63)	0.0381	0.57 (0.51)	0.2716
10 - 19	-5.17 (0.71)	<.0001	-0.69 (0.57)	0.2299
≥ 20	-8.80 (0.76)	<.0001	-3.71 (0.62)	**<.0001**

Notes: [a]Income level: low (<200% above poverty line), medium (200% to 400% above poverty line), high (>400% above the poverty line).
[b]Chronic physical condition is a binary value (No=not present, Yes=present) for the conditions listed in Appendix B.
The model fit was measured by its adjusted R^2 value (0.35).

Table 5. Unadjusted and Adjusted Regression Estimates (Beta) with Standard Errors (SE) of Significant Explanatory Variables Based on an Ordinary Least Squares Regression Model for Patient and Clinical Factors Associated with Mental Component Scores (MCS) in US Adult Cancer Survivors (≥ 18 years) for 2008, 2010, 2012, 2014 (N=10,076,059).

Explanatory Variables	*Unadjusted Model*		*Adjusted Model*	
	Beta (SE)	**P value**	**Beta (SE)**	**P value**
Polypharmacy				
Yes	-2.84 (0.43)	<.0001	-0.51 (0.51)	0.3145
Age Group (years)				
18-49	***Reference***			
50-64	1.21 (0.61)	0.0467	1.35 (0.58)	**0.0196**
65-74	3.40 (0.66)	<.0001	3.93 (0.69)	**<.0001**
≥ 75	3.05 (0.59)	<.0001	3.86 (0.71)	**<.0001**
Time Since Cancer Diagnosis (years)				
0-2	-1.78 (0.58)	0.0025	-1.64 (0.66)	**0.0133**
3-5	***Reference***			
6-10	-0.36 (0.46)	0.4358	-0.34 (0.61)	0.5691
≥ 11	-1.21 (0.51)	0.0178	-1.01 (0.71)	0.1514
Income Level[a]				
Low	-5.49 (0.52)	<.0001	-3.25 (0.53)	**<.0001**
Medium	-2.50 (0.54)	<.0001	-1.47 (0.49)	**0.0029**
High	***Reference***			
Insurance Coverage				
Private	***Reference***			
Public	-2.90 (0.49)	<.0001	-1.27 (0.50)	**0.0108**
Uninsured	-4.57 (1.20)	0.0002	-1.29 (1.12)	0.2473
Type of Cancer[b]				
Breast	1.08 (1.20)	0.3696	1.10 (1.15)	0.3354
Cervical/other female genital	-1.50 (1.31)	0.2546	0.85 (1.24)	0.4907
Colon/other gastrointestinal	-2.66 (1.29)	0.0413	-2.34 (1.13)	**0.0381**
Melanoma	1.84 (1.43)	0.2009	0.53 (1.21)	0.6619
Other/unspecified	0.08 (1.09)	0.9401	0.28 (1.02)	0.7843
Prostate/other male genital	2.42 (1.18)	0.0405	0.74 (1.15)	0.5224
Leukemias and Lymphomas	***Reference***			
Arthritis[c]				
Yes	-3.11 (0.46)	<.0001	-1.78 (0.41)	**<.0001**
Anxiety Disorders[d]				
Yes	-5.88 (0.73)	<.0001	-2.98 (0.67)	**<.0001**
Mood Disorders[d]				
Yes	-10.1 (0.68)	<.0001	-8.08 (0.67)	**<.0001**

Notes: [a]Income level: low (<200% above poverty line), medium (200% to 400% above poverty line), high (>400% above the poverty line).
[b]Type of cancer included the following categorizations: prostate (included testicular cancer and cancer of other male genitals), cervical (included uterine, ovarian, other female cancers), colorectal (esophageal, stomach, colon, rectum and anus, liver and intrahepatic bile duct, pancreas, and other gastrointestinal cancers).
[c]Arthritis is a binary value (Yes=present) and is listed in Appendix B.
[d]Anxiety and mood disorders are listed in Appendix B.
The model fit was measured by its adjusted R^2 value (0.22).

MANUSCRIPT 2

Title: Polypharmacy is associated with increased direct healthcare expenditures among cancer survivors in the United States.

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2.1 Abstract

PURPOSE: Prescription medications play a vital role in the lives of cancer survivors. However, they also contribute to rising healthcare expenditures in the United States (US). The objective of this study was to determine if polypharmacy (PP) is associated with increased healthcare expenditures among cancer survivors in the US.

METHODS: A cross-sectional study analysis of data from the Medical Expenditure Panel Survey (MEPS), a set of surveys of non-institutionalized individuals, households, their medical providers and employers throughout the US was conducted. The analytic sample included all patients 18+ years of age who had a diagnosis code for a single type of cancer, excluding nonmelanoma skin cancers, during even years 2008-2014. PP was defined as the reported use of ≥ 5 distinct therapeutic classes of prescribed medication during the panel (year). Healthcare expenditures were measured as the total direct payments per annum from all reported sources in 2017 dollars. We used ordinary least squares regression with log transformed expenditures as our dependent variable adjusting for various demographic and clinical variables.

RESULTS: PP was present in 43.9% (10.6 million, weighted per year) of cancer survivors included in this study. The per annum total direct medical expenditures for all cancer survivors in the US was $162.6 billion. The mean annual adjusted healthcare expenditures per cancer survivor with PP was $13,266 (SD $3,766), which was significantly higher than those without PP $8,753 (SD $5,082, p-value <.0001).

CONCLUSION: Cancer survivors with polypharmacy accounted for 70% of total annual medical expenditures among cancer survivors. PP was associated with higher expenditures across cancer types, intensity of utilization, and setting of care.

IMPLICATIONS FOR CANCER SURVIVORS: Cancer survivors should be aware that increased prescription medication use is associated with increased total healthcare expenditures.

2.2 Introduction

National health expenditures in the United States (US) increased by 3.9% from 2016 to 2017, and made up 17.9% of gross domestic product, totaling $3.5 trillion dollars according to the Centers for Medicare and Medicaid Services (CMS).[1] On average, this amounted to $10,739 per person in the US.[1] The estimated 2017 national expenditures on cancer care was $147.3 billion and is expected to increase to $157.8 billion in the Medicare population alone by 2020.[2]

Cancer was the sixth most expensive condition to treat in the US in 2015.[3] Most cancers are estimated to have a decreasing incidence and increasing survival rate for the foreseeable future.[2] A decreasing incidence may cause overall cancer-related expenditures to decline in the long run, but the prevalence of cancer coupled with the aging of the US population will result in an increase in the number of cancer survivors. Thus, increases in expenditures during treatment through end of life, the period of time which defines a cancer survivor,[4] are expected to continue to increase in coming years,[2] given that cancer survivors are estimated to increase from 15.5 million in 2016,[4] to 26.1 million by 2040.[5]

Cancer survivors face several major challenges including financial hardship, body image/self-esteem issues, and anxiety surrounding fears of long-term side-effects of treatment and cancer recurrence.[6] As part of some cancer survivors' treatment plans (e.g. breast cancer), they may take medications (adjuvant hormonal therapy) for the

following 5 to 10 years to lower the risk of recurrence.[7] Adjuvant therapy, for example, may increase the quantity of medications the survivor is to define them as having polypharmacy (PP), most commonly defined as the use of ≥ 5 concomitant medications.[8] Because survivors may have already been taking numerous medications to treat comorbid conditions and for palliative care one additional medication may now qualify as reaching the PP threshold.[9] PP is known to be highly prevalent and is associated with higher prescription costs among cancer survivors.[10]

The types of services and healthcare products cancer survivors require included in the national health expenditure estimates are hospital care, physician and clinical services, other professional services (specialists), dental services, home health care, nursing care facilities, medical equipment, prescription drugs, and various other services and products.[1] Hospital-based care comprised 33% of health spending (the largest percentage), whereas physician and clinical services made up 20%, and other health and personal care services totaled 5%, with the other groups (excluding prescription drugs) comprising the remainder.[1] Prescription drugs dispensed through retail pharmacies accounted for roughly 10% of the $3.5 trillion dollars spent on the total population for healthcare in 2017;[1] and expenditures on cancer treatments are expected to increase over time as new drugs tend to be more expensive than current standards of care.[11]

With prescription drugs comprising a significant portion of cancer-related expenditures, this study was conducted to examine the association between the

number of medications prescribed and healthcare expenditures among cancer survivors. The objective of this study was to expand current knowledge by examining the relationship between polypharmacy and direct healthcare expenditures. Quantifying the relationship between polypharmacy and healthcare expenditure in cancer is a requisite first step to understand the need for further study in determining to what degree increased healthcare expenditure is attributable to medication-related adverse events, or if polypharmacy is merely a proxy for burden of illness.

2.3 Methods

Study design and data source

We used a multi-year cross-sectional study design and utilized the Medical Expenditures Panel Survey (MEPS) database, a publicly available de-identified nationally representative database of the US.[12] The MEPS is a set of surveys containing nationally representative non-institutionalized persons, households (families and individuals), their medical providers, and employers throughout the US since 1996.[12] The MEPS uses a 2-year, 5-panel overlapping survey design of interviews.

We first used the medical conditions file to find individuals who reported cancer by using the cancer specific diagnosis codes through the Agency for Healthcare Research and Quality (AHRQ) clinical classification code system (Appendix A). We then linked the medical conditions, prescribed drugs, and household data files through a unique identifier for each individual cancer survivor.[12] We also used these clinical classification codes and the ICD-9-CM codes to identify concurrent chronic conditions using AHRQ's Elixhauser comorbidity codes.[13] Further details regarding the MEPS have been described elsewhere.[12]

Sample selection

The analytic sample included cancer survivors who were defined as adults (≥ 18 years old) with cancer who (1) responded 'Yes' to the MEPS survey question:

"Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?"; and (2) were alive at the end of the reference panel year. For our analyses we pooled data from years 2008, 2010, 2012, and 2014. In the MEPS, individuals are followed for two years, so to avoid including repeated observations we selected even years only. We excluded people with zero person-level sample weights and survivors with nonmelanoma skin cancer because treatment for basal and squamous cell carcinomas are often non-invasive compared to melanoma. Individuals also were excluded if they had more than one type of cancer due to the inability to determine an association between the person's total expenditures and one cancer type. Men with breast cancer were excluded because of small sample size and lack of generalizability to female breast cancer survivors. People under the age of 18, with missing age information, had an age at diagnosis greater than their reported age, or who died during the panel year were excluded. Figure 1 shows a flowchart of inclusion and exclusion criteria.

Measures

Dependent variable: Direct healthcare expenditures

Mean annual direct healthcare expenditures incurred per US cancer survivor was the dependent variable of interest. The expenditures represent the total direct payments from all reported sources to hospitals (facility and separately billed physicians), physicians, other medical, home health providers, for other providers, for dental providers, for miscellaneous expenses, and for prescriptions (Appendix C).[14] We created 5 distinct categories for expenditures: hospital, office-based, emergency

room, prescriptions, and other medical expenses. Hospital expenditures were the summation of the expenditures from the hospital outpatient visits and inpatient stays. Other medical expenditures included dental visits, home health providers (agency sponsored and paid independent provider), vision, and other medical expenses. Office-based, emergency room, and prescription expenditures were standalone categories within the MEPS. These expenditure groupings, when summed, equaled that of the total direct annual healthcare expenditures per cancer survivor.

Key independent variable

Polypharmacy (PP)

The MEPS include a prescriptions file with therapeutic medication class information which are linked to the Multum Lexicon database for analysis.[15] We used these therapeutic class details to determine the maximum number of distinct classes of prescription medications the individuals were on in one of the panels that coincided with our study years. A consensus definition of PP does not currently exist; however, the most common definition in the literature is 5 or more concomitant medications.[8] We chose 5 or more classes of medications as our definition for PP based on our review of the literature which included several studies which used classification classes.[16,17]

Other independent variables

Demographic variables included age group, sex, race/ethnicity, US geographic region (Northeast, South, Midwest, and West), and marital status (married or not

married). Socioeconomic variables included income (low, middle, high based on poverty level), insurance status (privately-, publicly-, or uninsured), and level of education (did not graduate high school, graduated but did not attend college, and at least some college level education). Time since cancer diagnosis was calculated by subtracting age at diagnosis, a variable included in the MEPS, from the patient's reported age. For patients who could not remember their age at diagnosis or was otherwise missing from the dataset, 51.7% total missingness, multiple imputation was used to fill in these missing values. We used the fully conditional specification (FCS) method, with all variables in the model creating 40 imputed data sets.[18] These data sets were then combined to get mean estimates across all variables.

Clinical variables included type of cancer, Elixhauser comorbidity score, and number of total provider encounters. Cancer type was grouped in the following manner: breast, prostate and other male genital (included testicular cancer), cervical and other female genital (included uterine, ovarian, other female cancers), colon and other gastrointestinal (GI) (stomach, liver, pancreas, and other GI cancers), melanoma, leukemias/lymphomas and other/unspecified (included lung). Lung cancer was grouped into the "other/unspecified" group due to small sample size. We used the Elixhauser comorbidity score to assess physical and mental diseases and disorders due to its well-established validity. The Elixhauser comorbidity score is the summation of approximately 31 comorbid conditions, which are first dichotomized as being present or absent in the patient, which we then categorized based on its distribution using quartiles to 0, 1, 2 or ≥ 3 (Appendix D).[13] Survivors with both complicated and

uncomplicated diabetes or hypertension diagnoses were assumed to have the complicated, more severe, state of disease for these analyses. Provider encounters were defined as total provider or outpatient visits obtained from the household files and categorized into 0-4, 5-9, 10-19, and ≥ 20 visits based on quartiles.

Statistical analysis

Significant differences in per-person mean annual direct expenditures between cancer survivors with and without PP were assessed using t-tests and analysis of variance (ANOVA), stratifying by type of cancer. Due to the positively skewed nature of the expenditures, a natural logarithm transformation was used to normalize the dependent variable. To fit a valid model for the log transformed expenditures we excluded patients with zero expenditures (n=28). A subgroup-specific smearing factor was applied after retransformation (exponentiation of beta estimate) to approximate nominal dollar values because without the smearing factor the estimates would be biased toward $0.[19] Expenditures were adjusted for inflation to 2017 US dollars using the Bureau of Labor Statistics consumer price index for medical care services.[20]

The primary analysis was to estimate the association between PP and total healthcare expenditures. Potential covariates were assessed in univariate OLS models for their statistical significance. If a variable was significantly associated with both PP and healthcare expenditures (F test p-value <0.10) it was included for assessment in a multivariable ordinary least squares (OLS) model. Multivariable (OLS) regression models were used to assess the relationship between PP and healthcare expenditures

while controlling for significant covariates. An iterative process was used to include individual covariates one at a time into the multivariable OLS model based on its F test p-value. If a covariate was insignificant after placement into the model it was removed, and the model was run again with the next covariate, until no more significant covariates remained for analysis.

In a secondary analysis, the relationships between PP and healthcare expenditures were modeled by setting of care overall, and by setting of care and type of cancer. Separate models were created for each of the log expenditures from the 5 settings of care as the dependent variables, controlling for all significant covariates from the primary analysis. OLS regression was used to analyze mean expenditures by PP for each setting overall. To estimate the mean expenditures for a woman with breast cancer, we first created a cohort of women with breast cancer, then we separately modeled the per-patient mean expenditures with each setting as a dependent variable. OLS regressions were used to find mean differences in expenditures by PP in both secondary analyses.

Due to the complexity of the survey design used in the MEPS; stratification, clustering, and weighting were performed. Significance tests were all performed at the $\alpha = 0.05$ level. Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

2.4 Results

The study population consisted of 3,435 (N= 10,580,285 weighted) adult cancer survivors (Figure 1, Table 1). The three most prevalent types of cancer were female breast (17.2%), prostate (14.0%, and melanoma (7.0%) (Table 1). Of these, 1,523 (N= 4,649,586 weighted, 43.9%) adults reported use of 5 or more therapeutic classes of prescribed medications. Older survivors (≥75 years) were most likely (60.8%) to have PP; while the youngest survivors (18-49 years) were least likely to have PP (18.4%). Most cancer survivors (54.0%) had at least 2 comorbid conditions, with over one-third (34.2%) having at least 3. Weighted percentages for all other demographic, socioeconomic, and clinical variables categorized as with or without polypharmacy are included in Table 2.

PP and prescription medication utilization

There were approximately 55 million (weighted) prescribed medications per year for the total cohort of cancer survivors: 72.5% (40.1 million (M)) of these prescriptions were to respondents defined as having PP (not shown). Those without PP were on 90 distinct therapeutic classes compared to 93 for those with PP. Of those therapeutic classes, 92.6% (88/95) were not unique between those without PP and those with PP. Antihyperlipidemic medications comprised the most commonly prescribed chronically used therapeutic class for both those with (7.0%; 2.8M weighted prescriptions) or without (9.2%; 1.4M) PP. Beta-adrenergic blocking agents

were the second most prevalent therapeutic class in those with PP (4.5%; 1.8M) (Table 3).

Overall expenditure differences by PP

The unadjusted and untransformed mean per-patient direct healthcare expenditures for the overall study cohort was $15,369 (95% CI: $14,146-$16,591). The total per year expenditures averaged $162.6 billion, adjusted to 2017 dollars. Those with PP accounted for 70.3% of the total annual mean expenditures. The total annual mean expenditures were $21,652 (95% CI: $18,485-$24,820) for those with PP and $13,414 (95% CI: $9,952-$16,875) for those without PP, resulting in a significantly different (p-value <.0001) mean difference of $8,239 (Table 4).

Total mean annual expenditures by setting of care and PP

Mean annual adjusted expenditure in the hospital setting was the largest contributor to total annual expenditures for cancer survivors (Figure 2). Expenditures for cancer survivors in the hospital setting amounted to $68.8 billion (B) (standard deviation: SD $22.9B) annually and comprised 42.3% of total spend by setting. Hospital-based expenditures accounted for 42.0% ($21.9B SD $9.7B) of $52.1B (SD $13.8B) total annual expenditures for cancer survivors without PP. For those with PP, hospital-based expenditures comprised 42.5% ($47.0B SD $21.3B) of $110.5B (SD $28.2B) total expenditures per year. Prescription medicines for all cancer survivors made up 19.9% ($32.3B SD $6.7B) of total annual expenditures. For survivors with PP, prescriptions made up 76.5% ($24.7B SD $5.1B) of total annual expenditures

compared to 23.5% ($7.6B) for those without PP. Other medical expenditures totaled 8.6% ($14.0B SD $7.4B) of total annual expenditures by setting. Survivors with PP accounted for 71.4% ($10.0B SD $7.4B) of other medical expenditures. Emergency room expenditure accounted for 2.3% ($3.7B SD $2.1B) and was the smallest contributor to total annual mean expenditures in both those with polypharmacy and those without PP (2.3% ($2.6B SD $1.9B) and 2.2% ($1.1B SD $527M), respectively).

Expenditure differences by setting of care and PP

Table 4 shows the smear-adjusted log transformed mean expenditures for each setting of care by PP. Mean expenditures were higher for each setting, except for office-based visits, with the highest average mean expenditures being spent in the hospital setting for those with PP ($12,314 95% CI: $9,981-$15,040). However, differences in mean expenditures by PP for both office-based ($2,350 CI: 2,126-$2,571 vs. $2,410 CI: $2,203-$2,637 p-value 0.3146) and emergency room ($2,444 CI: $2,021-2,927 vs. $1,598 CI: $1,308-$1,952 p-value 0.0921) settings were not significantly different than for those without PP.

Expenditure differences by type of cancer, setting of care, and PP

Figure 3 presents the results from smear-adjusted OLS analyses of mean transformed expenditures by settings of care and type of cancer by PP status, which controlled for significant variables. Across all types of cancer, except for melanoma ($7,709 vs. $16,922, p-value 0.4739), expenditures in the hospital setting for survivors

with PP were higher than for those without PP. However, only leukemias & lymphomas and other/unspecified cancer types were significantly higher in those with PP than without PP ($19,114 vs. $8,742 p-value 0.0048 and $12,964 vs.8,943 p-value 0.0073, respectively). For office-based care, mean expenditure differences were significantly higher in those with PP for only the other/unspecified cancer type ($2,296 vs. $2,069 p-value 0.0206). Emergency room mean differences for expenditures were significantly higher in survivors with PP and leukemias and lymphomas ($2,437 vs. $641, p-value 0.0067), melanoma ($765 vs. $403, p-value <.0001), and the other/unspecified cancer categories ($3,330 vs. $1,689, p-value 0.0471). Mean expenditures differences between the other medical category were significantly different for breast cancer ($2,242 vs. $1,036 p-value 0.0088) and colorectal ($4,955 vs. 1,505 p-value .0243). For each type of cancer, the modeled values for prescription medication expenditures were significantly higher (p-value <0.0001) in all survivors with PP compared to those without PP.

Associations between PP and healthcare expenditures

As seen in Table 5, PP was significantly associated with higher total annual mean log expenditures (β= 0.60, SE=0.05, p-value <.0001) when controlling for all significant variables (age, insurance, cancer type, comorbidity, provider encounters, and time since cancer diagnosis). This estimate represents an 82% increase in the total annual mean log expenditures due to a one-unit increase of the average number of cancer survivors having PP, holding all other variables at their reference class.

Several covariates had significant differences from their referent group in their association with total annual mean expenditures. All types of cancer examined, except for cervical and other female genital cancers, were significantly different from melanoma in their association with log expenditures while controlling for PP, age, insurance, time since cancer diagnosis, comorbidity, and provider encounters (Table 5). Colon and other GI cancers was the most significantly different (β= 0.57, SE 0.11, p-value <.0001) from melanoma (reference group) with a 76% increase in mean log expenditures. Survivors with ≥ 3 comorbid conditions had a significant 37% increase from those without any comorbidities (β= 0.31, SE 0.06, p-value= <.0001). Survivors with public insurance (β= -0.12, SE 0.04, p-value= 0.0023) and without any insurance (β= -0.42, SE 0.14, p-value= 0.0029) were associated with lower mean log expenditures than survivors with private insurance (12% and 34%, respectively). Those aged 50-64 were significantly different from their referent group of 18-49 years (β= 0.19, SE 0.06, p-value= 0.0014) with an associated 20% increase in mean log expenditures. Lastly, the number of visits to a provider was progressively significant and by far the most associated with increased mean log expenditures, with ≥ 20 encounters having a 540% increase in mean log expenditures (β= 1.85, SE 0.08, p-value <.0001) (Table 5). Time since cancer diagnosis of 2 years or less was significantly different in mean log expenditures compared to cancer survivors of 3 to 5 years by an increase of 36% (β= 0.31, SE 0.08, p-value <.0001).

After applying the subgroup-specific smear factors to the retransformed (exponentiated) estimates of the adjusted mean expenditures, the annual expenditure

for someone with PP was $13,226 (SD $3,766), which was $4,513 more than survivors without PP at $8,753 (SD $5,082), and was significant (p-value <.0001). The log expenditure estimates, subgroup-specific smearing factors, and final adjusted values are presented in Table 6.

2.5 Discussion

In this study, we found that approximately 44 of 100 adult cancer survivors per year were defined as having PP. PP was associated with significantly higher mean annual direct healthcare expenditures in all analyses, including unadjusted, adjusted, and our log transformed multivariable OLS model. Unadjusted total mean expenditures for cancer survivors in our study were higher than the 2012 estimated expenditures reported by AHRQ for the general population by 89% ($15,369 vs. $8,125, respectively).[21] For survivors with PP, the unadjusted difference in mean expenditures was associated with an increase of 70% in spending, with annual spend equaling $21,652 compared to $13,414 for survivors without PP. In the adjusted analysis, PP was associated with a significant 82% increase in the estimated log expenditures compared to those without PP.

By comparing the various settings of care for cancer survivors, we found that spending in the hospital setting is higher compared to the other settings, for both those with and without PP, which aligns with prior research.[1] Hospitalization has been linked to increased medication use in older cancer patients.[9,22] However, hospital-based expenditures for those both with or without PP were approximately 42% of spend by setting, higher than that in the general population (33%).[1] The largest differences for cancer survivors with versus without PP by setting were office-based (23.7% vs. 33.7%, respectively) and prescription medications (22.4% vs. 14.6%, respectively). These amounts were also higher as a proportion of spending by setting

compared to the general population (20% for office-based and 10% for prescription medication).[1] We combined expenditures from both inpatient and outpatient hospital visits while other studies have categorized hospital costs based solely on inpatient hospitalizations versus ambulatory (outpatient) hospital visits and office-based visits.[23] This may be why hospital-based expenditures were so much higher than office-based visits in this study. Our analysis provides further evidence that cancer survivors have substantially greater direct healthcare expenditures than the general population.

Differences existed among the different types of cancers, regarding overall healthcare expenditures for those with PP compared to those without PP. In the adjusted analyses, where we controlled for all significant variables, total annual mean expenditures for those with colon or other GI cancers were the highest, although not statistically significant from other cancer types. In a 2016 study of the economic burden (defined as annual medical expenditures plus annual productivity losses) of colorectal, female breast, and prostate cancer survivors in the US, which also used the MEPS (years 2008-2012), colorectal cancer was associated with the highest annual expenditures and productivity losses of the three cancer types.[23]

Various risk factors for PP among cancer patients include comorbid conditions, hospitalization, and unnecessary prescribing.[9] Most cancer survivors in the current study had at least 2 comorbid conditions. When examined closer by PP, 6% of those without a chronic condition were defined as having PP; while 78.2% of those with ≥ 3 conditions had PP. In the log transformed expenditure model, having ≥3 comorbid

conditions was associated with a 37% increase in expenditures compared to not having any comorbid conditions. Due to the cross-sectional study design, we cannot determine causality, but there was a clear association between PP and expenditures. Future research that focuses on the examination of individual comorbid conditions and the number of prescriptions an individual are on both pre- and post- cancer diagnosis would elucidate this relationship further, as it was not the emphasis of this research.

We identified one paper that examined healthcare expenditure differences among cancer survivors with PP, in which they estimated median prescription expenditures as $1,633 vs. $784 in noncancer controls, but did not analyze total expenditure values.[10] Knowing that prescription costs significantly differ among cancer survivors with PP, as well as noncancer counterparts with PP, is important for addressing disparities among cancer survivors with and without PP. One reason for the disparities is that spending on anticancer medications doubled from 2012-2017 to almost $50 billion, with all oncology drugs launched in 2017 having list prices above $100,000.[24] In the US, the cancer drug market is expected to grow 12-15% annually by 2020, up to $100 billion.[24] This growth is expected to be driven by new launches and increased uptake of existing branded oncologics.[24] However, one positive trend is that oncology drug prices have risen at a slower rate (4.7%-6.4%) on average than that of the general branded market (6.9%) from 2012-2017.[24] We chose to incorporate total healthcare expenditures by PP among cancer survivors to see differences at the person and societal levels. In so doing, we hope that policymakers could be informed about how influential PP is on the healthcare system in the US.

This study determined that the total annual expenditure estimates for US cancer survivors for the period of 2008-2014, adjusted to 2017 dollars was $162.6 billion. According to research which used SEER-Medicare data, the estimated costs of cancer care will equal $157.8 billion by 2020.[25] However, when taking into consideration the declining incidence for most cancers, improving survival rates, and increasing costs, the authors estimated the total cost could amount to $172.8 billion.[25] Our estimate concurs with this as it is in the upper range of these two estimates.

Increased healthcare costs can have negative effects on both the individual cancer survivor and society as a whole.[26] For cancer survivors, concerns over outcomes previously linked to PP include adverse drug events, drug-drug interactions, increased morbidity, decreased survival, frailty/disability, and poor medication adherence.[9] On the societal level, policymakers may have to address the increased expenditures related to prevention initiatives and various adverse health-related outcomes in this expanding vulnerable population. PP may cause increased healthcare expenditures because of additional therapeutic monitoring, lab tests, physician office visits, and follow-up care planning.

Currently in the US, the focus of various advocacy and governmental groups focuses on lowering the cost of prescription medications. Although this is certainly needed, for cancer survivors whom are mostly covered by private or public insurances,

a closer look at hospital and office-based expenditures should also be highly scrutinized due to the largest proportions of expenditures being spent in those areas.

2.6 Limitations

As this was a cross-sectional study design, no claim of causality can be made. Other limitations may exist due to the way the data was collected, through computerized survey. Recall bias may have impacted the answers to the survey as some respondents may not have an accurate recollection of life events due to various reasons (e.g. older age, responding for another household member). The MEPS uses a 3-digit coding system for ICD-9-CM codes, and thus the nuances of certain comorbid conditions may not be recorded. Likewise, using the Elixhauser comorbidity score dichotomizes conditions and does not consider differences in severity of comorbid conditions. No severity or stage of cancer for the survivors is recorded which would otherwise explain large differences in expenditures of survivors of the same type of cancer. For this analysis, based on sample sizes of individual cancers, we grouped various cancers together which may obfuscate more precise expenditure differences among those survivors.

2.7 Conclusion

Mean total annual expenditures for cancer survivors with PP was significantly higher than for those without PP, with significant differences attributable to setting of care, intensity of utilization, and type of cancer. Understanding this association is the first step to addressing the underlying causes of expenditure differences among those cancer survivors with versus without PP.

2.8 References

1. National Health Expenditure 2017 Highlights. Centers for Medicare & Medicaid Services. Available Online: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NationalHealthAccountsHistorical.html. Accessed December 17, 2018.

2. Mariotto AB, Robin Yabroff K, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst. 2011 Jan 19;103(2):117-28. doi: 10.1093/jnci/djq495. Epub 2011 Jan 12. Erratum in: J Natl Cancer Inst. 2011 Apr 20;103(8):699. PubMed PMID: 21228314; PubMed Central PMCID: PMC3107566.

3. Agency for Healthcare Research and Quality. Total expenditures in millions by condition, United States, 2015. Medical Expenditure Panel Survey. Generated interactively: Tue Apr 02 2019.

4. NCI Dictionary of Cancer Terms was originally produced by the National Cancer Institute. Available Online: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/survivorship. Accessed December 17, 2018.

5. Bluethmann SM, Mariotto AB, Rowland, JH. Anticipating the "Silver Tsunami": Prevalence Trajectories and Comorbidity Burden among Older Cancer Survivors in the United States. Cancer Epidemiol Biomarkers Prev. 2016 Jul;25(7):1029-36. doi: 10.1158/1055-9965.EPI-16-0133. PubMed PMID: 27371756; PubMed Central PMCID: PMC4933329.

6. American Cancer Society. Transitioning Back to Life After Treatment Is a Challenge for Many Cancer Survivors: Researchers are finding new ways to help. Last reviewed: March 21, 2017. Online Available: https://www.cancer.org/latest-news/transitioning-back-to-life-after-treatment-is-a-challenge-for-many-cancer-survivors.html. Accessed February 28, 2019.

7. Lu CY, Zhang F, Wagner AK, Nekhlyudov, Earle CC, Callahan M. Impact of high-deductible insurance on adjuvant hormonal therapy use in breast cancer. Breast Cancer Res Treat. 2018 Aug;171(1):235-242. doi: 10.1007/s10549-018-4821-z. Epub 2018 May 12. PubMed PMID: 29754304; PubMed Central PMCID: PMC6231999.

8. Masnoon N, Shakib S, Kalisch-Ellett L, Caughry GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr. 2017 Oct 10;17(1):230. doi: 10.1186/s12877-017-0621-2. Review. PubMed PMID: 29017448; PubMed Central PMCID: PMC5635569.

9. Hersch LR, Beldowski K, Hajjar ER. Polypharmacy in the Geriatric Oncology Population. Curr Oncol Rep 2017 Sep 23;19(11):73. doi: 10.1007/s11912-017-0632-3. Review. PubMed PMID: 28942563.

10. Murphy CC, Fulling HM, Alvarez CA, Betts AC, Lee SJC, Haggstrom DA. Polypharmacy and patterns of prescription medication use among cancer survivors. Cancer. 2018 Jul 1;124(13):2850-2857. doi: 10.1002/cncr.31389. Epub 2018 Apr 12. PubMed PMID: 29645083; PubMed Central PMCID: PMC6147245.

11. Cancer Statistics was originally produced by the National Cancer Institute. Available Online: https://www.cancer.gov/about-cancer/understanding/statistics. Accessed December 17, 2018.

12. Medical Expenditure Panel Survey; Agency for Healthcare Research and Quality. Available: https://meps.ahrq.gov/mepsweb/. Accessed February 16, 2018.

13. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36(1):8–27 [Epub 1998/02/07].

14. Machlin S, Soni A, Fang Z. Understanding and analyzing MEPS household component medical condition data. Available Online: https://meps.ahrq.gov/survey_comp/MEPS_condition_data.shtml. Accessed November 7, 2018.

15. Agency for Healthcare Research and Quality. Medical Expenditure Panel Survey, HC-135A: 2010 Prescribed Medicines; 2012. https://meps.ahrq.gov/data_stats/download_data/pufs/h135a/h135adoc.pdf. Accessed November 7, 2018.

16. Meraya AM, Dwibedi N, Sambamoorthi U. Polypharmacy and Health-Related Quality of Life Among US Adults With Arthritis, Medical Expenditure Panel Survey, 2010-2012. Prev Chronic Dis. 2016 Sep 22;13:E132. doi: 10.5888/pcd13.160092. PubMed PMID: 27657504; PubMed Central PMCID: PMC5034554.

17. Vyas A, Babcock Z, Kogut S. Impact of depression treatment on health-related quality of life among adults with cancer and depression: a population-level analysis. J Cancer Surviv. 2017 Oct;11(5):624-633. doi: 10.1007/s11764-017-0635-y. Epub 2017 Aug 10. PubMed PMID: 28799098.

18. Liu Y, De A. Multiple imputation by fully conditional specification for dealing with missing data in a large epidemiologic study. Int J Stat Med Res. 2015;4(3):287-295.

19. Manning WG. The logged dependent variable, heteroscedasticity, and the retransformation problem. J Health Econ. 1998; 17(3): 283-95.

20. US Bureau of Labor Statistics. Labor Price Index: CPI databases. Accessed December 15, 2018.

21. Soni A. Top Five Most Costly Conditions among Adults Age 18 and Older, 2012: Estimates for the US Civilian Noninstitutionalized Adult Population. Statistical Brief #471. April 2015. Agency for Healthcare Research and Quality, Rockville, MD. http://www.meps.ahrq.gov/mepsweb/data_files/publications/st471/stat471.shtml.

22. Nobili A, Licata G, Salerno F, et al. Polypharmacy, length of hospital stay, and in-hospital mortality among elderly patients in internal medicine wards. The REPOSI study. Eur J Clin Pharmacol. 2011 May;67(5):507–19. doi: 10.1007/s00228-010-0977-0. Epub 2011 Jan 11. PubMed PMID: 21221958.

23. Zheng S, Yabroff KR, Guy Jr GP, et al. Annual Medical Expenditure and Productivity Loss Among Colorectal, Female Breast, and Prostate Cancer Survivors in the United States. J Natl Cancer Inst. 2015 Dec 24;108(5). doi: 10.1093/jnci/djv382. Print 2016 May. PubMed PMID: 26705361; PubMed Central PMCID: PMC4849808.

24. IQVIA Institute for Human Data Science. Global Oncology Trends 2018: Innovation, Expansion and Disruption. May 2018. Available Online: https://www.iqvia.com/institute/reports/global-oncology-trends-2018. Accessed January 3, 2019.

25. Yabroff KR, Lund J, Kepka D, Mariotto A. Economic burden of cancer in the US: estimates, projections, and future research. Cancer Epidemiol Biomarkers Prev. 2011 October; 20(10): 2006–2014. doi10.1158/1055-9965.EPI-11-0650.

26. Balducci L, Goetz-Parten D, Steinman MA. Polypharmacy and the management of the older cancer patient. Ann Oncol. 2013 Oct;24 Suppl 7:vii36-40. doi: 10.1093/annonc/mdt266. PubMed PMID: 24001761; PubMed Central PMCID: PMC6278993.

Figure 1. Selection of Patients for Analyses of Prevalence of Polypharmacy in Adult Cancer Survivors (≥ 18 years) (2008, 2010, 2012, 2014), Unweighted.

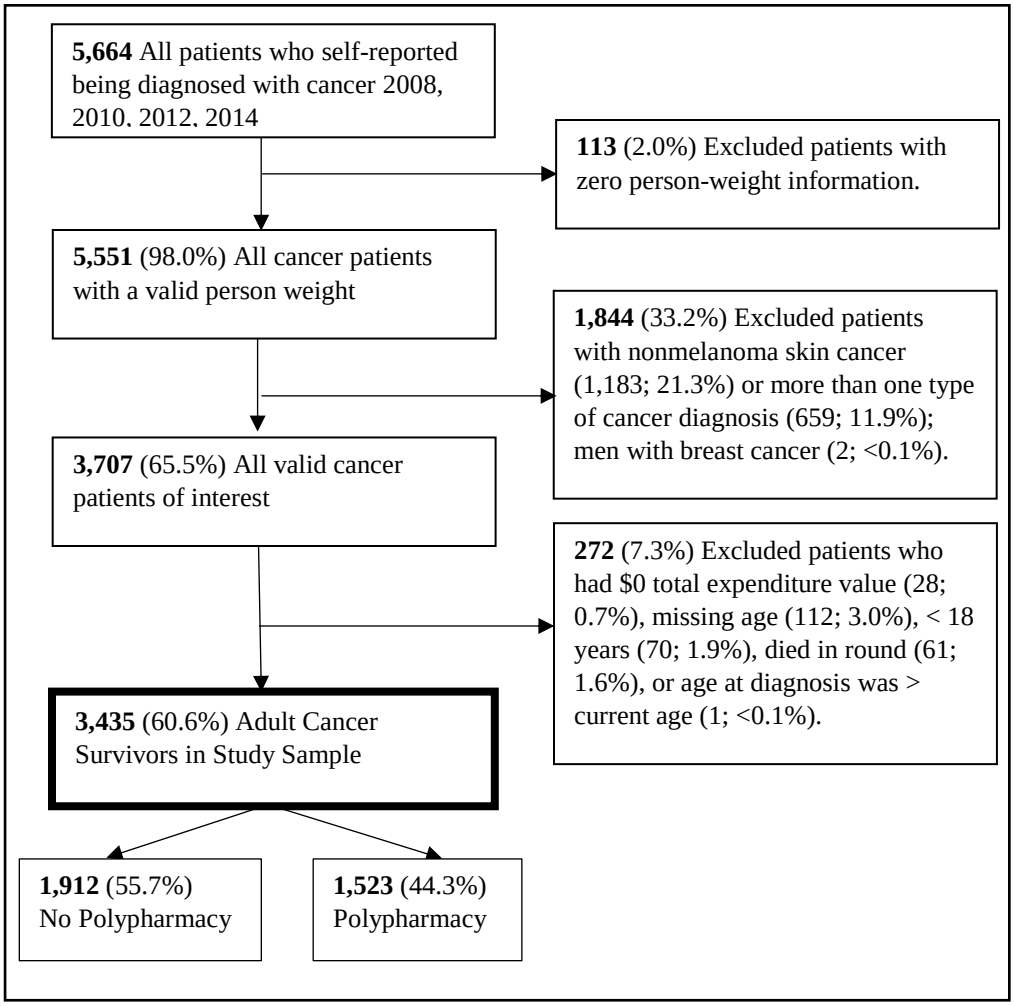


Table 1. Distribution of Cancer Diagnoses in Adult Cancer Survivors (≥ 18 years) (2008, 2010, 2012, 2014) of Interest Available in MEPS.

Type of Cancer	N (%), unweighted	N, weighted
Breast	613 (17.2%)	1,820,759
Prostate and other male genital	484 (14.0%)	1,486,297
Cervical and other female genital	228 (5.7%)	607,562
Colon and other GI	250 (6.4%)	673,767
Melanoma	193 (7.0%)	741,584
Leukemias and lymphomas	160 (4.7%)	493,481
Other / unspecified	1,507 (45.0%)	4,756,835
Total	**3,435 (100.0%)**	**10,580,285**

Table 2. Demographic and Clinical Characteristics of Adult Cancer Survivors (≥ 18 years) with Cancer Diagnoses of Interest during 2008, 2010, 2012, 2014, by Polypharmacy Status (N= 10,580,285).

Demographic and Clinical Characteristics of Cancer Survivors	No Polypharmacy (N= 5,930,699 | 56.1%)	Polypharmacy (N= 4,649,586 | 43.9%)	p-value
Age group (years)[a]			<.0001
18-49	1,746,353 (81.6%)	393,978 (18.4%)	
50-64	2,019,881 (60.3%)	1,327,615 (39.7%)	
65-74	1,222,852 (45.5%)	1,467,364 (54.5%)	
≥ 75	941,613 (39.2%)	1,460,629 (60.8%)	
Sex			0.8300
Men	2,619,191 (55.8%)	2,073,216 (44.2%)	
Women	3,311,508 (56.2%)	2,576,370 (43.8%)	
Race/ethnicity			0.0109
White	4,819,924 (55.8%)	3,824,725 (44.2%)	
African American	415,971 (50.4%)	409,089 (49.6%)	
Hispanic	429,810 (63.6%)	245,621 (36.4%)	
Other	264,994 (60.9%)	170,151 (39.1%)	
Region			0.0158
Northeast	1,232,839 (57.7%)	904,430 (42.3%)	
Midwest	1,224,135 (52.8%)	1,096,576 (47.2%)	
South	2,002,800 (53.1%)	1,770,205 (46.9%)	
West	1,470,925 (62.6%)	878,375 (37.4%)	
Provider Encounters			<.0001
≤ 4	1,914,471 (81.6%)	432,042 (18.4%)	
5 - 9	1,773,239 (64.9%)	957,942 (35.1%)	
10 - 19	1,407,070 (48.0%)	1,524,128 (52.0%)	
≥ 20	835,919 (32.5%)	1,735,474 (67.5%)	
Marital Status			0.0168
Married	3,723,611 (58.0%)	2,694,351 (42.0%)	
Not Married	2,207,088 (53.0%)	1,955,235 (47.0%)	
Education Level			<.0001
Less than High School	2,661,512 (52.9%)	2,374,522 (47.1%)	
High School	943,463 (50.6%)	920,694 (49.4%)	
Some College	2,325,724 (63.2%)	1,354,370 (36.8%)	
Income Level[b]			<.0001
Low	1,378,526 (46.4%)	1,593,485 (53.6%)	
Medium	1,555,858 (55.4%)	1,250,218 (44.6%)	
High	2,996,315 (62.4%)	1,805,883 (37.6%)	
Insurance Coverage			<.0001
Private	4,428,221 (59.9%)	2,958,484 (40.1%)	
Public	1,179,479 (42.0%)	1,631,759 (58.0%)	
Uninsured	322,999 (84.5%)	59,343 (15.5%)	
Type of Cancer[c]			0.0597
Breast	946,815 (52.0%)	873,945 (48.0%)	
Prostate/other male genital	787,573 (53.0%)	698,724 (47.0%)	
Cervical/other female genital	377,641 (62.2%)	229,921 (37.8%)	
Colon/other gastrointestinal	338,687 (50.3%)	335,080 (49.7%)	
Melanoma	448,397 (60.4%)	293,187 (39.6%)	
Leukemias and lymphomas	255,124 (51.7%)	238,358 (48.3%)	
Other/unspecified	2,776,462 (58.4%)	1,980,371 (41.6%)	
Time since cancer diagnosis (years)			0.0014
0-2	1,056,198 (58.2%)	759,676 (41.8%)	
3-5	1,071,483 (58.1%)	773,356 (41.9%)	
6-10	1,964,487 (58.3%)	1,404,582 (41.7%)	
> 10	1,838,531 (51.8%)	1,711,972 (48.2%)	

Elixhauser Comorbidity[d]			<.0001
0	2,209,455 (94.9%)	118,926 (5.1%)	
1	1,921,954 (75.6%)	621,467 (24.4%)	
2	1,010,014 (48.3%)	1,083,265 (51.7%)	
≥ 3	789,276 (21.8%)	2,825,929 (78.2%)	

Notes: [a]The Medical Expenditures Panel Survey sets an upper limit of 85 years old.
[b]Income level: low (<200% above poverty line), medium (200% to 400% above poverty line), high (>400% above the poverty line).
[c]Type of cancer included the following categorizations: prostate (included testicular cancer and cancer of other male genitals), cervical (included uterine, ovarian, other female cancers), colorectal (esophageal, stomach, colon, rectum and anus, liver and intrahepatic bile duct, pancreas, and other gastrointestinal cancers).
[d]Elixhauser Comorbidity Score: The summation of a binary variable (Present/Absent) for each of the comorbid conditions in the group of conditions (Appendix D).

Table 3. Top 10 Most Frequently Prescribed Therapeutic Classes among Patients with and without Polypharmacy, in US Adult Cancer Survivors (≥ 18 years) for 2008, 2010, 2012, 2014 (N=10,580,285) weighted n, %.

No Polypharmacy			Polypharmacy		
Therapeutic Class	**Rx (n)**	**Rx (%)**	**Therapeutic Class**	**Rx (n)**	**Rx (%)**
Antihyperlipidemic Agents	1,395,299	9.2%	Antihyperlipidemic Agents	2,809,821	7.0%
Thyroid Hormones	693,981	4.6%	Beta-Adrenergic Blocking Agents	1,794,952	4.5%
Antidepressants	680,754	4.5%	Antidepressants	1,607,836	4.0%
Beta-Adrenergic Blocking Agents	548,796	3.6%	Angiotensin Converting Enzyme Inhibitors	1,608,534	4.0%
Angiotensin Converting Enzyme Inhibitors	524,150	3.4%	Proton Pump Inhibitors	1,558,512	3.9%
Dermatological Agents	519,554	3.4%	Diuretics	1,461,365	3.6%
Proton Pump Inhibitors	503,199	3.3%	Antidiabetic Agents	1,421,401	3.5%
Antihypertensive Combinations	459,858	3.0%	Anticonvulsants	1,264,175	3.2%
Antidiabetic Agents	415,267	2.7%	Thyroid Hormones	1,132,490	2.8%
Diuretics	408,366	2.7%	Bronchodilators	914,132	2.3%

Notes: Rx(n) = Total weighted number of prescribed therapeutic classes to cancer survivors on average for the years 2008, 2010, 2012, 2014. Rx(%) = Average annual number of prescribed therapeutic classes as a weighted percentage of total average annual by polypharmacy.

Figure 2. Expenditures Among US Adult Cancer Survivors (≥ 18 years) by Setting of Care and Polypharmacy for 2008, 2010, 2012, 2014, (%).

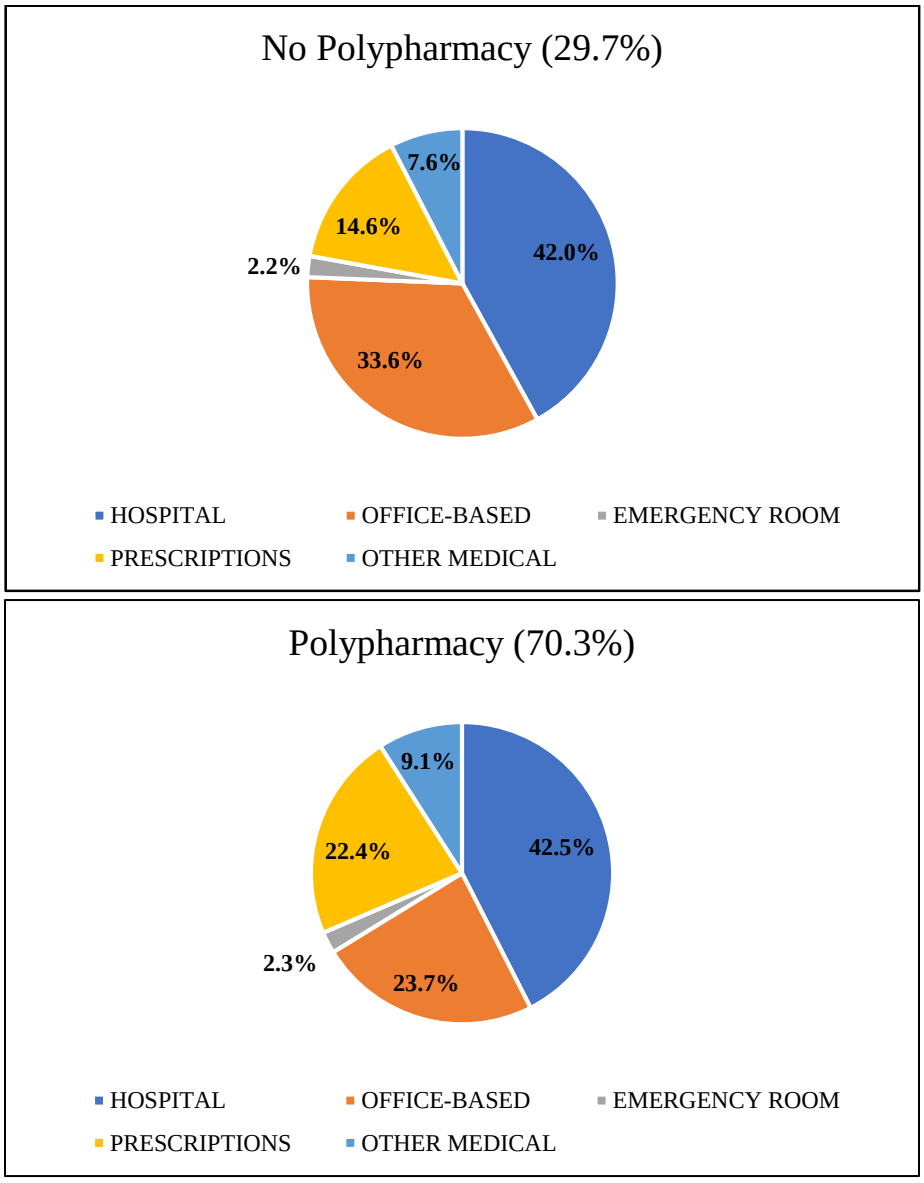
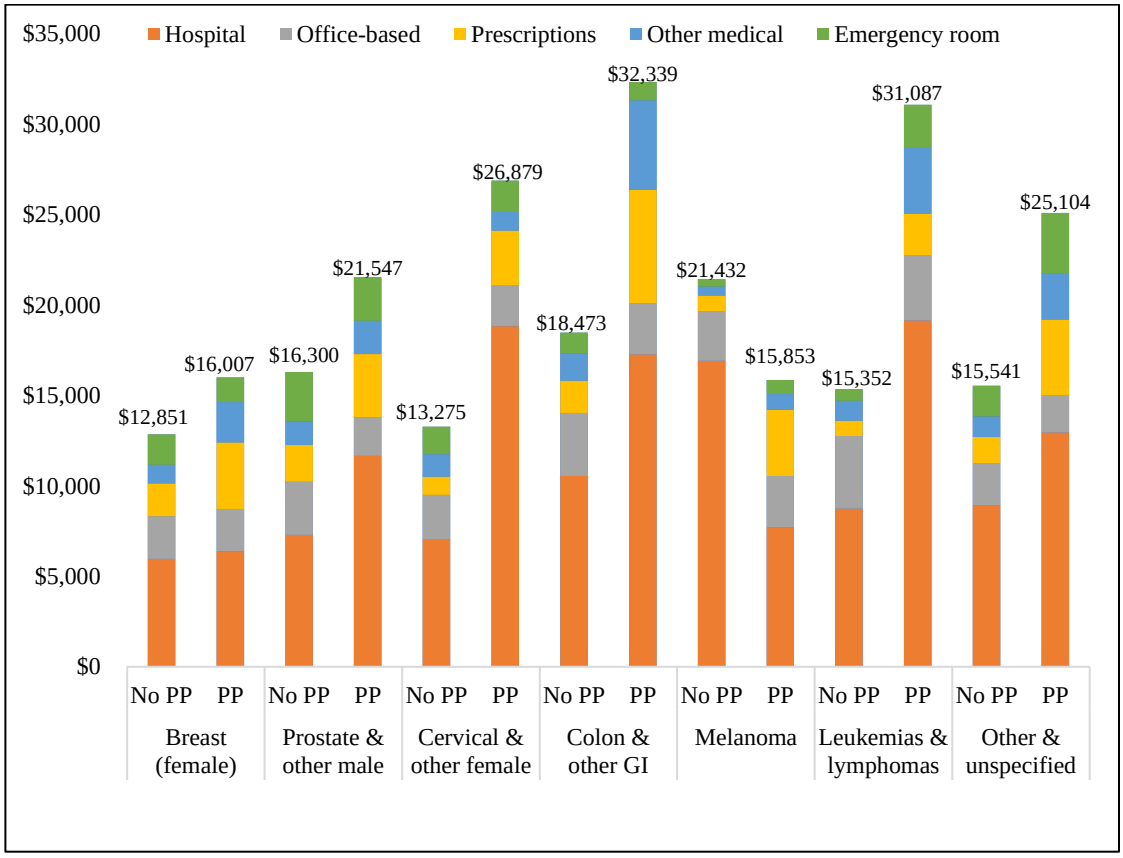


Table 4. Adjusted Mean Annual Total Expenditures by Setting of Care and Polypharmacy, in US Adult Cancer Survivors (≥ 18 years) for 2008, 2010, 2012, 2014 (N=10,580,285), Weighted ($US)

Settings of Care	Mean (95% CI), $US		p-value	Mean Difference ($)
	No Polypharmacy	Polypharmacy		
Hospital	9,398 (7,542 - 11,829)	12,314 (9,981 - 15,040)	0.0018	2,915
Prescriptions	1,709 (1,531 - 1,908)	4,056 (3,707 - 4,483)	<.0001	2,347
Office-based	2,410 (2,203 - 2,637)	2,350 (2,126 - 2,571)	0.3146	(60)
Other medical	1,127 (1,030 - 1,233)	2,447 (2,192 - 2,759)	<.0001	1,320
Emergency room	1,598 (1,308 - 1,952)	2,444 (2,021 - 2,927)	0.0921	846

Notes: Values are adjusted variables significantly associated with log expenditures and may include a combination of any of the following variables: age group, gender, race, region, number of provider encounters, marital status, comorbidity score, education level, poverty level, and insurance coverage.
*Values are rounded to nearest whole dollar value or percent where applicable.

Figure 3. Results of Ordinary Least Squares Regression Describing Adjusted Mean Log Expenditures for Each Type of Cancer among US Adult Cancer Survivors (≥ 18 years) by Setting of Care and Polypharmacy for 2008, 2010, 2012, 2014 (N=10,580,285), ($US)



	Breast		Prostate		Cervical		Colon	
Setting	**No PP**	**PP**	**No PP**	**PP**	**No PP**	**PP**	**No PP**	**PP**
Hospital	5,971	6,390	7,294	11,675	7,058	18,839	10,543	17,273
Office-based	2,353	2,339	2,937	2,127	2,441	2,249	3,503	2,844
Prescriptions	1,815	3,673*	2,038	3,486*	1,016	3,041*	1,786	6,249*
Other medical	1,036	2,242*	1,294	1,854	1,238	1,015	1,505	4,955*
Emergency room	1,676	1,363	2,737	2,405	1,522	1,735	1,136	1,018

Melanoma		Leukemia/Lymphoma		Other	
No PP	**PP**	**No PP**	**PP**	**No PP**	**PP**
16,922	7,709	8,742	19,144*	8,943	12,964*
2,725	2,837	4,016	3,605	2,296*	2,069
887	3,663*	852	2,313 *	1,463	4,178*
492	879	1,101	3,678	1,150	2,563
406	765 *	641	2,347*	1,689	3,330*

Note: No PP = no polypharmacy; PP = polypharmacy. Hospital = inpatient or outpatient hospital-based expenditure. Emergency = Emergency Room. Prescriptions = prescription medications. Other medical = sum of spending for the following: dental care, vision care, home health agency (sponsored and paid independent providers), and other expenses not classified elsewhere. Estimates are adjusted for the following variables: age group, gender, race, region, number of provider encounters, marital status, comorbidity score, education level, poverty level, and insurance coverage. Gender was excluded from cervical, prostate, and breast cancer models. *= significantly increased expenditures compared within PP / No PP pairing at alpha = 0.05 significance.

Table 5. Unadjusted and Adjusted Regression Estimates (β) with Standard Errors (SE) of Significantly Associated Variables Based on an Ordinary Least Squares Regression Model with Log Transformed Expenditures for Patient and Clinical Factors in US Adult Cancer Survivors (≥ 18 years) for 2008, 2010, 2012, 2014 (N=10,580,285).

Studied Variables	***Unadjusted Model***		***Adjusted Model***		
	Beta (SE)	**P value**	**Beta (SE)**	**Change (%)**	**P value**
Polypharmacy					
Yes	1.23 (0.04)	<.0001	0.60 (0.05)	82.0	**<.0001**
Age Group (years)					
18-49	***Reference***				
50-64	0.65 (0.08)	<.0001	0.19 (0.06)	20.4	**0.0014**
65-74	0.77 (0.08)	<.0001	0.04 (0.06)	4.6	0.4834
≥ 75	0.87 (0.08)	<.0001	0.08 (0.07)	8.7	0.2587
Insurance Coverage					
Private	***Reference***				
Public	0.07 (0.06)	0.2467	-0.12 (0.04)	-11.6	**0.0023**
Uninsured	-1.15 (0.17)	<.0001	-0.42 (0.14)	-34.3	**0.0029**
Type of Cancer[a]					
Breast	0.41 (0.12)	0.0008	0.20 (0.09)	21.8	**0.0034**
Cervical/other female genital	0.06 (0.16)	0.6948	0.21 (0.11)	23.4	0.0518
Colon/other gastrointestinal	0.71 (0.15)	<.0001	0.57 (0.11)	76.3	**<.0001**
Leukemias and lymphomas	0.53 (0.18)	0.0033	0.40 (0.13)	48.7	**0.0015**
Other/unspecified	0.20 (0.12)	0.0834	0.21 (0.09)	23.9	**0.0135**
Prostate/other male genital	0.34 (0.12)	0.0057	0.27 (0.10)	31.1	**0.0070**
Melanoma	***Reference***				
Elixhauser Comorbidity Index (no. of conditions)					
0/None	***Reference***				
1	0.54 (0.08)	<.0001	0.10 (0.06)	11.0	0.1014
2	0.83 (0.08)	<.0001	0.14 (0.07)	15.2	**0.0441**
≥ 3	1.38 (0.07)	<.0001	0.31 (0.06)	36.8	**<.0001**
Provider Encounters (no. of visits)					
0 - 4	***Reference***				
5 - 9	0.84 (0.07)	<.0001	0.68 (0.07)	99.6	**<.0001**
10 - 19	1.54 (0.07)	<.0001	1.23 (0.07)	247.8	**<.0001**
≥ 20	2.30 (0.07)	<.0001	1.85 (0.08)	547.1	**<.0001**
Time since cancer diagnosis (years)					
0-2	0.35 (0.08)	<.0001	0.31 (0.08)	35.7	**<.0001**
3-5	***Reference***				
6-10	0.07 (0.06)	0.2299	0.06 (0.07)	6.6	0.3618
>10	0.11 (0.05)	0.0287	0.03 (0.07)	2.9	0.6793

Notes: [a]Type of cancer included the following categorizations: prostate (included testicular cancer and cancer of other male genitals), cervical (included uterine, ovarian, other female cancers), colorectal (esophageal, stomach, colon, rectum and anus, liver and intrahepatic bile duct, pancreas, and other gastrointestinal cancers). Adjusted R^2 value for final model equaled 0.46. Model intercept equaled 7.05 (SE=0.12).

Table 6. Subgroup-Specific Smear Adjusted Mean Annual Direct Healthcare Expenditures, with or without Polypharmacy, in US Adult Cancer Survivors (≥ 18 years) for 2008, 2010, 2012, 2014 (N=10,580,285).

Polypharmacy	Log Transformed Expenditure Estimate (ln(β))	Standard Error	Retransformed Expenditure Estimate (exp^{β}, $US)	Subgroup-Specific Smearing Factor	Smear Adjusted Expenditure Estimate, ($US)
No	8.3930	0.05151	4,416	1.98199	8,753
Yes	8.9916	0.05626	8,035	1.65097	13,266

Note: Adjusted R^2 value for final OLS model was 0.46. Mean differences of log transformed expenditure estimates was significant ($p<.0001$). The subgroup-specific smearing factors were calculated as the mean of the exponentiated residuals. Smear-adjusted expenditure estimate is the product of the retransformed expenditure estimate and the subgroup-specific smearing factor. Adjusted for age, type of cancer, insurance coverage, comorbidity score, time since cancer diagnosis, and number of provider encounters.

MANUSCRIPT 3

Title: Association between polypharmacy and nonfatal health complications in newly diagnosed patients with breast, prostate, lung, or colorectal cancers in the United States.

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3.1 Abstract

BACKGROUND: Patients with cancer are particularly susceptible to polypharmacy (PP), which may increase the risk of developing health complications (HCs). The objective of this study was to evaluate the association between PP and nonfatal HCs among newly diagnosed patients with common cancer types in the United States (US).

METHODS: We conducted a retrospective cohort study of de-identified, newly diagnosed adult (≥ 18 years old) breast, prostate, lung and colorectal cancer patients using the Optum Clinformatics® DataMart (Optum, Eden Prairie, MN, USA) administrative claims database, years 2010-2015. PP was defined as ≥ 5 distinct therapeutic classes of medications filled through an outpatient pharmacy in the first quarter following patients' index cancer diagnosis. The dependent variable was nonfatal HCs (none vs. ≥ 1 event). HCs were grouped by clinically meaningful category: cardiovascular (CV), central nervous system and psychiatric (CNS), gastrointestinal (GI), hematologic (HEMA), metabolic (METB), skeletal (SKEL), and miscellaneous drug-related events (ADE). We used multivariable logistic regression (LR), with adjusted odds ratios (aORs) with 95% confidence intervals (CI) as the measure of effect to examine associations between PP and HCs in patients with cancer overall, and by type of cancer, controlling for demographic and physical and mental comorbid conditions.

RESULTS: The analytic cohort consisted of 35,336 individuals with cancer (breast 14,700, prostate 15,706, colorectal 3,292, and lung 1,638). PP was present in 14,573 (41.2%) of individuals. Percentage of PP by type of cancer were: breast 42.7%, prostate 37.0%, colorectal 43.7%, lung 64.0%. Individuals with PP had higher rates of

HCs compared to those without PP: CV 19.2% vs. 8.9%, CNS 5.2% vs. 2.4%, GI 2.8% vs. 1.6%, HEMA 9.9% vs. 5.5%, METB 3.8% vs. 1.1%, SKEL 5.6% vs. 3.5%, and ADE 3.0% vs. 1.4%, during follow-up. In the primary analysis, PP was associated with a 31% increased odds (aOR) of having ≥ 1 HCs, controlling for age, region, type of cancer, comorbidities, radiation and chemotherapy treatments. PP was significantly associated with a higher risk of having ≥ 1 HC in each cancer type (aOR: breast 1.37, 95% CI: 1.31-1.42; prostate 1.27, CI: 1.22-1.32; colorectal 1.26, CI: 1.16-1.36; lung 1.25, CI: 1.11-1.40). Active chemotherapy was associated with significantly increased odds of ≥ 1 HC in colorectal (aOR: 1.35, CI: 1.21-1.50) and lung (aOR: 1.33, CI: 1.15-1.54) cancers, but not significantly associated with breast or prostate cancers.

CONCLUSIONS: Newly diagnosed patients with breast, prostate, colorectal, or lung cancer with PP were all at a higher risk of having ≥ 1 nonfatal HCs as compared to those without PP. Active chemotherapy treatment was associated with increased risk of HCs in colorectal and lung cancer patients, but not in breast or prostate cancer patients.

2.2 Introduction

PP is defined most commonly in the literature as the concomitant use of ≥ 5 medications,[1] and one study found that 80% of newly diagnosed elderly (≥ 65 years) cancer patients met this criterion.[2] Patients with cancer often receive many medications,[3] regularly exceeding the numerical threshold for polypharmacy (PP). Reasons for the multitude of prescribed medications in cancer patients are usually rooted in underlying chronic conditions occurring naturally with aging.[4] For instance, 32.2% of older women (> 66 years) newly treated for breast cancer have comorbidities.[5] With the median ages at diagnosis for the four most common types of cancer in the United States (US) being 61 years for breast cancer, 68 years for colorectal cancer, 70 years for lung cancer, and 66 years for prostate cancer, comorbid conditions are common in this population.[6] Comorbid conditions in patients with cancer can influence the treatment care planning.[4] For example, women with breast cancer may not receive certain types of chemotherapy if comorbid conditions sufficiently increase the risk of complications.[5]# However, depending on stage of cancer and other factors, women may still receive additional medications such as hormone therapy or pain relievers, in addition to medicines they take for underlying conditions.

Some cancer patients may, or may not, be using 5 prescribed medications at the time of their diagnosis. However, during the course of treatment for cancer, they may add new medications resulting in PP. One concern which arises from PP among

older patients is the increased risk associated with use of potentially inappropriate medications (PIMs) that may have a deleterious effect on the patient's health. PP has been associated with PIMs previously.[7,8,9] PIMs are concerning for cancer patients as one study found that, of newly diagnosed cancer patients who visited ambulatory oncology clinics, the odds of using PIMs increased by 18% for each additional medication in those defined as having PP (≥ 5 concomitant medications) compared to those without PP.[10] Common cancer-related ailments such as pain, emesis, depression, venous thrombosis, and seizures can also necessitate additional medications.[10]

The increased use of combinations of medications also increase the risk of drug-drug interactions (DDIs) among cancer patients, even among those not currently receiving antineoplastic treatments.[1] DDIs can result in a lack of effectiveness of one or all the drugs, enhance toxicity, and diminish a treatment's intended outcome.[11] Potential underlying risk factors for DDIs in cancer patients include mucositis and malnutrition causing impaired absorption, edema resulting from changes in a drug's volume of distribution, or excretion changes from renal and/or hepatic dysfunction.[12] Other factors include a patient's age, narrow therapeutic index of the drugs involved, and physiologic make-up.[13] DDIs may lead to various negative outcomes, including new health complications among patients with cancer,[13] and falls resulting in fractures which may cause delays in cancer treatments and alter the trajectory of the disease, care planning, or prognosis.[14]

A health complication (HC) is defined in this study similarly to an adverse event, as a possible negative outcome resulting in patient harm or injury due to use of prescribed medications,[15] including medication errors, adverse drug reactions, allergic reactions, and overdoses.[16]

To the authors' knowledge, PP associated with HCs in newly diagnosed cancer patients have not been thoroughly investigated in a large administrative claims database. The primary objective of this study was to estimate and describe the frequency of HCs in newly diagnosed cancer patients, with or without polypharmacy, in a multivariable framework.

3.3 Methods

Study design and data source

We conducted a retrospective cohort study to estimate the associated risk (odds) of having ≥ 1 health complication (HC) with PP among newly diagnosed adult cancer patients, controlling for various demographic attributes and clinical characteristics of those patients. The data source used was Optum Clinformatics® DataMart (Optum, Eden Prairie, MN, USA), years 2010-2015. The database contains de-identified claims information with the following data tables: eligibility of privately-insured members, medical inpatient and outpatient professional services, inpatient services, outpatient prescription dispensings, and inpatient facility details. Patients were linked through a common identifier across the various claims tables to ensure all encounters are captured. The database is comprised of approximately 35 million unique commercially-insured patients in the US and their captured medical encounters.

Sample selection

The study population included adult individuals (≥ 18 years old) with an incident diagnosis of cancer (breast, prostate, colorectal, and lung) who had continuous enrollment in medical and prescription insurance throughout a 12-month lookback period through the end of follow-up for the first year following cancer diagnosis. Female breast, prostate, colorectal, and lung cancer cases were selected for our study because they are considered the four major cancers by the American Cancer

Society.[14] A patient had to have at least 2 cancer diagnosis claim codes (including in situ and metastasis), defined by the International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM) classification system, in the primary or secondary diagnosis field, which were at least 30 days apart in either the outpatient or inpatient setting (Appendix E). The patient's first cancer diagnosis was their index date. Patients with claims of a personal history of cancer within one year prior to their first ICD-9-CM code matching were excluded from the algorithm. Individuals were excluded if their incident diagnosis was not between January 1, 2011 and September 30, 2014. Men with breast cancer were excluded because the focus was on the four most commonly occurring cancers in the US. If an individual did not have any pharmacy claims in the year of follow-up they were excluded. People with more than one type of cancer were excluded, except those with metastatic codes to capture advanced stage diagnoses. Patients with less than one full year of data following incident diagnosis were excluded, including those who died. Figure 1 shows the inclusion and exclusion criteria in greater detail.

The key independent variable (IV) of interest was PP, defined as a patient filling ≥ 5 distinct medication classes at an outpatient pharmacy in the first quarter (3 months) following incident cancer diagnosis, not accounting for overlap or switching, with a cumulative sum of days' supply of at least 7 days, during the 3-month exposure window after the index date. Since no clear definition of PP exists in the literature,[2] we chose our definition based on published literature which used distinct therapeutic classes.[17,18] These factors, coupled with other research which stated that no single cut-

point was optimal in defining PP in cancer patients,[19] but that ≥ 5 daily medications was a reasonable threshold for predicting multiple adverse events in elderly cancer patients, informed our decision to use ≥ 5 therapeutic classes as our threshold for PP. However, to examine medication use with more accuracy and in a shorter time period than the aforementioned study, we used a claims database study. Medication classes were categorized using the American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic classification system.[20] Vaccinations, due to one-time administrations, and vitamin (A-E), due to their tendency to be more over-the-counter, medication classes were excluded from this definition.[21]

Dependent variable

The primary outcome variable of interest was nonfatal health complications (HCs), and was dichotomized to either 0 (zero) HCs or ≥ 1 HC. HCs consisted of both specifically coded adverse drug-related events (ADEs) and other health conditions that are often associated with adverse effects of medications (e.g. organ toxicity, blood dyscrasias, falls). HCs were grouped into the following clinically meaningful categories: cardiovascular (CV), central nervous system and psychiatric (CNS), gastrointestinal (GI), hematologic (HEMA), metabolic (METB), skeletal (SKEL), and miscellaneous adverse drug-related events (ADE). The categories were curated from published literature based on their relevance to patients with cancer, PP, or both.[22,23] The outcomes selected were based on current literature and have been either (1) well documented in cancer patients,[15,22,23,24,25,26,27,28,29,30,31] and/or (2) were considered more likely in people with PP.[32,33,34,35,36] The goal of choosing these outcomes was to

provide a selective list of short-term events which could have been precipitated by the combination of drugs in a population with a lowered immune system, mostly elderly (≥ 65), and who may have been increasing their medications due to anticancer treatment. Clinical events related to common drug interactions in one study included deep vein thrombosis, upper digestive hemorrhage, various other forms of bleeding, and neutropenia.[15] Other studies mentioned the risk of falling in elderly due to PP,[47] or in those with cancer because of the risk to treatment delays and potential cancer-related outcomes as a result.[30,33] Other examples of specific HCs include fractures and arrhythmias (See appendix H for full list). HCs were measured in patients with cancer by using a claims-based algorithm searching for these complications using ICD-9-CM diagnosis codes. As part of the inclusion criteria, patients had to have continuous enrollment in both medical and prescription claims for the year following their incident diagnosis, thus they were alive throughout follow-up. The follow-up period in which these HCs were measured was during the 3 quarters following the exposure period (quarter 1) in which the presence of PP was determined.

Covariates

Demographic covariates were assessed during the 12-month baseline period and included age, sex, and geographic region. Clinical variables assessed at baseline included type of cancer, insurance plan-type, and Elixhauser comorbidity score. Radiation and chemotherapy treatments were assessed after exposure. Cancer type was grouped in the following manner: breast (female only), prostate, lung, and colorectal using the ICD-9-CM codes listed in Appendix E. We chose to use the Elixhauser

comorbidity score, excluding the 3 codes related to cancer, to assess physical and mental diseases and disorders based on the variety of ailments contained within, and its well-established validity.[37] The Elixhauser comorbidity score is the summation of various comorbid conditions which are dichotomized to represent a condition's presence (1) or absence (0) (Appendix F). We categorized the scores based on the overall distribution into 3 categories 0, 1-2, ≥ 3 conditions. Patients with both complicated and uncomplicated diabetes, or hypertension, diagnoses claims were assumed to have the more complicated stage of the disease for these analyses. This method was used to prevent double counting of the disease if a patient had both claims. Anticancer infusions and injections were identified using Healthcare Common Procedure Coding System (HCPCS) coding system in the outpatient setting (J codes J8500-J9999). The HCPCS coding system classifies similar medical products into categories for efficient claims processing.[38] If the individual received either an outpatient pharmacy prescription and/or a J code for an antineoplastic agent during the year following their incident diagnosis, they were defined as receiving active chemotherapy. Radiation was defined through Current Procedural Terminology (CPT) and HCPCS G codes (Appendix G).[39,40]

Statistical analysis

Descriptive statistics were used to describe the proportions of cancer patients by PP for each covariate. Chi-square tests were used to determine the statistical significance between PP and categorical covariates, as well as between PP and HCs.

Also, the percentages of PP in patients with a HC were described according to the type of cancer. Lastly, to provide information on the number and percent of different medication drug classes filled by those with or without PP, the 20 most filled medication drug classes were described.

Logistic regression (LR) modeling was used to examine associations between individual covariates and HCs. Variables which had statistically significant (p-value <0.10) association with both PP and HC were used in the multivariable LR modeling process. The multivariable LR model examined the relationship between PP and HCs, controlling for the covariates which were significantly related to both PP and HC in the univariate LR models. Collinearity amongst covariates was assessed by examining the condition indices and variance decomposition proportions.[41] However, no two independent variables were collinear and thus no variables were removed at this stage.

Covariates were added to the model sequentially based on their negative 2 Log Likelihood statistic (-2 Log L). Model comparisons were assessed through the Likelihood Ratio Test (LRT) which produced comparison statistics among models based on their intercept and covariates using the -2 Log L, where a better fitting model had a lower -2 Log L value.[41] A manual stepwise elimination process was used to remove variables with p-values higher than 0.05 significance to determine which of the remaining variables were still significant in the multivariable model. Lastly, comparison between model performance were assessed by changes in Akaike Information Criteria (AIC), and goodness-of-fit was tested by changes in c-statistic

(concordance index) values.[42] The measure of effect was the adjusted odds ratio (aOR) comparing the risk (odds) that a person having PP experienced a HC versus those without PP, controlling for all other significant covariates.

The objective of a secondary analysis was to examine the relationship among PP with HCs by type of cancer, controlling for significant covariates (Table 3). To understand the relationship, four models were created (one for each cancer type) by first including the following covariates: sex (only for colorectal and lung cancers), age, region, insurance, comorbidity score, radiation therapy, and chemotherapy treatment. In these analyses, a manual backward elimination process was used to remove covariates that were not significant. First, the variable with the largest p-value (> 0.05) was removed. Next, the model was reanalyzed to determine if any of the remaining covariates became or remained insignificant. If a variable was insignificant (p-value >0.05) it was removed. This process was continued until only significant variables remained in the model. All statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3.4 Results

The analytic cohort consisted of 35,336 adult cancer patients (Figure 1). Of these, 14,573 (41.2%) adults were defined as having PP in the first quarter following incident cancer diagnosis (Table 1). The cohort had the following characteristics: men (51.2%), ≥ 65 years (61.8%), were not actively on chemotherapy (68.3%) or radiation therapy (79.8%) and had ≥ 1 comorbid condition (68.8%). Of those with PP, 70.5% were ≥ 65 years, 52.5% were women, 43.1% had breast cancer, 37.4% were on chemotherapy, 19.9% received radiation therapy and 42.2% had ≥ 3 comorbid conditions (Table 1). In total, 8,891 (25.2%) people with cancer had ≥ 1 HC in the follow-up period (Table 1). Of those, 4,963 (34.1%) had at least 1 HC in the 3 quarters during follow-up.

The proportion of adult cancer patients with PP and ≥1 HC as compared with those who did not have PP were significantly higher (p-value < .0001) across all HC groups (Table 1). The proportion of patients with PP and ≥ 1 cardiovascular (CV) event was 19.2% compared to patients without PP who had ≥ 1 CV event (8.9%). The other differences in proportions were as follows: CNS 5.2% vs. 2.4%, GI 2.8% vs. 1.6%, HEMA 9.9% vs. 5.5%, METB 3.8% vs. 1.1%, SKEL 5.6% vs. 3.5%, and ADE 3.8% vs. 2.4%, per year during follow-up. All counts and percentages for this analysis are presented in Table 1. All differences were statistically significant at the alpha = 0.05 level.

Prescription medications

A total of 155,735 prescriptions were filled during the exposure window (Table 2). Of those, 107,619 (69.1%) were filled by those defined as having PP. The 20 most filled medication classes amounted to 63.9% of total fills for those without PP compared with 54.4% in the PP group. The classes of medications were similar in both groups, with HMG-CoA reductase inhibitors being filled the most for PP (7.3% of fills for PP) and no PP (9.8% of fills for No PP). For the 20 most filled medications, differences existed between those with and without PP for a handful of classes. For example, loop diuretics (1.7%), sulfonylureas (1.6%), anticonvulsants (1.6%), and metformin (1.5%) were top 20 filled medications by people with PP, but not those without PP. Conversely, first generation cephalosporins (2.0%), corticosteroids (1.4%), aminopenicillins (1.3%), and anti-inflammatory (skin) agents (1.2%) were in the top 20 for those without PP, but not those with PP.

Health complications

Figure 3 highlights percentage of patients with ≥1 HC by type of cancer, with or without PP. Regardless of cancer type, patients with ≥1 HC had a higher percentage of PP. Patients with lung cancer and HCs had the highest percentage of PP (73.1%). Conversely, men with prostate cancer and ≥1 HC had the lowest percentage of PP (51.2%).

Presented in Figure 4 are the percentages of HCs by PP for each type of cancer. Across each type of cancer CV complications occurred the most, with HEMA

HCs as the second most frequent. Differences between PP and no PP groups were statically significant at p-value < 0.05 for each cancer type, with the exception of GI in colorectal and lung, and skeletal in lung.

Primary analysis: association between PP and nonfatal HCs

To determine the association between PP and nonfatal HCs in the analytic cohort, a multivariable LR model was created controlling for age, region, type of cancer, comorbidity burden, radiation therapy, and chemotherapy (Figure 4). Excluded from this analysis were sex (due to the gender-specific nature of breast and prostate cancers) and insurance type (due to its insignificance during the model building process described in the Methods section). PP was associated with a 31% increase in the risk of having ≥ 1 HC (aOR 1.31, 95% CI: 1.27-1.35, p-value <.0001) in the follow-up period when controlling for the covariates. Breast and prostate cancers were significantly associated with decreased risk of having ≥ 1 HC compared to colorectal cancer (aOR 0.83, 0.79-0.87, p-value <.0001 and aOR 0.84, 0.81-0.87, p-value <.0001 respectively). Whereas lung cancer had a significantly increased risk for ≥ 1 HC compared to colorectal cancer (aOR 1.23, 1.13-1.23, p-value <.0001).

Chemotherapy and radiation treatments were both significantly associated with a slightly increased risk of having ≥ 1 HC in the final multivariable LR model (aOR 1.07, 1.03-1.10, p-value <.0001 and aOR 1.06, 1.02-1.10, p-value= 0.0012, respectively). Age ≥ 75 years old was significantly associated with an increased risk of having the outcome of interest compared to those aged 50-64 years (aOR 1.39, 1.33-

1.45, p-value <.0001). The Northeast was significantly associated with an increase in risk of having ≥ 1 HCs compared to those in the Midwest (aOR 1.08, 1.02-1.14, p-value= 0.0088). Figure 4 presents additional results pertaining to comorbidity level and use of chemotherapy or radiation.

Secondary analysis: associations between PP and HCs by type of cancer

Four multivariable logistic regression models were created to assess the association between PP and HCs for each type of cancer (Table 3). As mentioned previously, sex was excluded as an explanatory variable from the analysis for breast and prostate cancers, due to those cancers being sex-specific. Across all four models PP, age, and comorbidity were significant predictors of HCs. The association between PP and ≥ 1 HC and other main findings by type of cancer are described next.

In the model for women with breast cancer, PP was associated with a 37% increase in the odds of having ≥ 1 HC in the follow-up period (aOR 1.37, 1.31-1.42, p-value <.0001) compared to those without PP. Each age group was significantly different from those aged 50-64 years old, with the oldest having a 26% increase in risk (aOR 1.26, 1.17-1.35, p-value <.0001). The West was the only region significantly different from the Midwest and associated with a decreased risk of having ≥ 1 HC by 18% (aOR 0.82, 0.77-0.88, p-value <.0001). The number of comorbid conditions and radiation therapy were significant, but chemotherapy was not (Table 3).

In the model for prostate cancer, PP was associated with a 27% increase in the risk of having ≥ 1 HC (aOR 1.27, 1.22-1.32, p-value <.0001). Younger age (18-49 years) was associated with a 35% decreased risk of ≥ 1 HC (aOR 0.65, 0.51-0.83, p-value = 0.0004); whereas the oldest aged group (≥ 75 years) had a significantly higher risk (aOR 1.71, 1.55-1.88, p-value <.0001) compared to those aged 50-64 years. Each region was significantly different from the Midwest, with the Northeast associated with an increased risk of ≥ 1 HC (aOR 1.12, 1.02-1.23, p-value = 0.0143). Similar to breast cancer, chemotherapy was not significantly associated with HCs. Unlike breast cancer, radiation therapy was insignificant. Table 3 includes findings for age, region, comorbidity level, chemotherapy, and radiation.

PP was associated with 26% increase in the risk of having ≥ 1 HC (aOR 1.26, 1.16-1.36, p-value <.0001) in people with colorectal cancer when controlling for age, region, comorbidities, and chemotherapy. Unlike breast and prostate cancers, chemotherapy was significantly associated with an increased risk of having the outcome of interest for those with colorectal cancer (aOR 1.35, 1.21-1.50, p-value <.0001). Age followed the same pattern as prostate cancer, where younger age was associated with a decreased risk of having ≥ 1 HC (aOR 0.61, 0.49-0.75, p-value <.0001), and older age was associated with an increased risk (aOR 1.73, 1.52-1.97, p-value <.0001). Table 3 includes findings for age, sex, region, comorbidity level, chemotherapy, and radiation.

Lastly, for those with lung cancer, PP was associated with a 25% increased risk of ≥ 1 HC (aOR 1.25, 1.11-1.40, p-value =0.0002). Unique to those with lung cancer was the significant increased risk associated with the person's sex. Men were 22% more likely to have ≥ 1 HC compared to women (aOR 1.22, 1.10-1.36, p-value = 0.0002). Both chemotherapy (aOR 1.33, 1.15-1.54, p-value <.0001) and radiation treatment (aOR 1.25, 1.10-1.36, p-value = 0.0188) were associated with increased odds of having ≥ 1 HC. Unlike the other cancer types, the analyzed regions were not associated with a significant difference in risk for people with lung cancer compared to the Midwest. Model fit (c-statistic) values for each are presented in the notes section at the bottom of Table 3.

3.5 Discussion

We used a large administrative claims database to describe the association between PP and the risk of having ≥ 1 HCs among newly diagnosed patients with breast (female), prostate, lung, and colorectal cancer controlling for significant covariates (age, sex, radiation therapy, chemotherapy, comorbid conditions, and geographic region). We also estimated associations between each type of cancer and HCs controlling for those covariates. In each multivariable LR model, PP was associated with a greater than 25% increase in the risk of having ≥ 1 HC.

Polypharmacy

In our study, we found that greater than 40% (2 in 5) of adult patients with newly diagnosed breast, prostate, colorectal, and lung cancers were defined as having PP in the first quarter following diagnosis. One study, which defined PP as ≥ 5 distinct medications, reported the prevalence of PP to be 64% in cancer survivors; however, this was a cross-sectional study with a more liberal definition of polypharmacy, which summed the medications used over two years.[43] Three studies reported the overall prevalence of PP in newly diagnosed cancer patients to be 80% (patients aged ≥ 65 years in US),[3] 57% (in patients aged ≥ 70 years in Australia),[44] and 35% (patients also ≥ 70 years in Denmark).[45] However, all studies varied in their setting and collection methods. In the study that reported overall PP of 35%, lung cancer had the highest percentage of patients with PP (40.9%), compared to the other types of cancer: 32.9% (breast), 29.9% (colorectal), and 32.3% (prostate).[45] These rates were slightly lower

than our results; however, that study was a case-control study where the controls did not have a cancer diagnosis at the index date. Although we did not have the same study design or source population, our results showed that PP, by type of cancer, was also highest in patients with lung cancer (64.0%).

PP was associated with a significantly higher risk of having ≥ 1 HC in all analyses, including unadjusted and adjusted LR models. By grouping HCs, we found that cancer patients with PP had higher proportions of HCs for different body systems compared to those without PP. For example, complications involving the cardiovascular system were more than double (19.2%) in patients with PP compared to those without PP (8.9% p-value <.0001). A study by Barber et al found that certain hormone therapies in breast and prostate cancer patients increased cardiac arrhythmias.[24] In a review of the impact chemotherapy has on cardiac arrhythmias, Tamargo et al reported inducement of a direct cardiac effect that can also be initiated or maintained by substrates created by comorbid conditions or the chemotherapy.[25] Hematologic HCs were the second most common, with 9.9% of patients with PP having at least one compared to 5.5% in those without PP. The hematologic HCs included in this study are well-established outcomes in patients with cancer; especially venous thromboembolisms and pulmonary embolisms which are known to increase after surgery and chemotherapy treatment.[26]

The results of the primary analysis showed that PP was highly significant in its association with the risk of having HCs by 31% when controlled for age, region, type

of cancer, comorbidity, chemotherapy, and radiation therapy. This means that patients with PP, which comprise 40% of those newly diagnosed with the four most common types of cancer, have a 31% higher risk of health complications overall. Polypharmacy has been associated with increased use of potentially inappropriate medications, which can cause adverse health outcomes among older patients. According to a study by Lund et al, which analyzed the Surveillance, Epidemiology, and End Results (SEER)-Medicare database, among 19,318 breast, 7,283 colon, and 7,237 lung cancer patients age 66 years and older, the number of PIMs changed after initial diagnosis of cancer during follow-up (6-23 months duration).[27] The increase in PIM dispensing was directly related to chemotherapy initiation in the first six months. They reported that for women with breast cancer PIMs decreased, while those with colon or lung cancer saw an increase. In our analysis, a decreased aORs for breast cancer patients, and increased aORs for lung, compared to the reference group (colorectal cancer) may be caused by a similar PIM risk. Lund et al did not study prostate cancer, but with the watchful-waiting or active surveillance approach recommended by the National Comprehensive Cancer Network (NCCN), a lack of additional medications for treatment may also decrease the risk of PIMs and thus decrease the odds of HCs.[46]

The secondary analysis of PP among cancer types revealed cancer-specific differences for PP and some of the covariates. PP had the largest estimated risk in breast cancer patients of the four main cancers, with an increased risk of 37%. One explanation for this may be the influence of the covariates, specifically that chemotherapy was not significantly associated with HCs. Lund et al found that of

19,318 newly diagnosed patients with stage I-III breast cancer, PIMs declined (40% to 34%) after diagnosis and leveled off as chemotherapy use was curtailed beginning 3 months after incident diagnosis until 23-months follow-up.[27] For women with early stage breast cancer, they often receive surgery followed by radiation then hormone therapy, but not chemotherapy.[47] According to Edwards et al, women with any number of comorbid conditions are less likely to receive chemotherapy compared to those who have none.[48] Therefore, for the women who receive chemotherapy, they may have an advanced stage of breast cancer, and the risk of complications would not be significantly different. Our results showed that women between the ages of 65 and 74 years had a lower risk of HCs compared to those 50-64 years and this lack of chemotherapy may be why. As chemotherapy is not recommended for early stages of breast cancer in adults over 70,[48] or with having a high number of comorbidities, our findings suggest that these newly diagnosed breast cancer patients were in situ or invasive, but not metastatic. Whereas, those aged ≥ 75 years had the highest number of comorbid conditions (38.5%: not shown) compared to the reference group which had the largest percentage without comorbidity (35.5%: not shown). Also, radiation therapy was associated with more HCs which is logical since side-effects linked to radiation therapy may lead to exacerbating underlying conditions. The youngest age group was associated with a higher risk for HCs, which could be explained by 58% (not shown) of those aged 18-49 having no comorbidities, indicating they may have had a more aggressive form of cancer, as 59% of those aged 18-49 received chemotherapy treatment compared to 56.0% in the reference group. This higher rate of chemotherapy may have directly led to an increase in HCs.

Patients with prostate cancer and PP had a 27% increased risk of having ≥ 1 HC when controlling for age, region, and comorbidity score. Like patients with breast cancer, chemotherapy was not significantly different between those who had ≥ 1 HC and those who had none during follow-up. One explanation would be that men with prostate cancer tend to be diagnosed in their late 60s and early 70s, and the median age in this study was 69 years. Standard of care for patients with low-risk prostate cancer thus does not usually involve chemotherapy but may include hormone therapy. Radiation therapy was also not significantly associated with the outcome of interest. Differences in HCs from those 50-64 years old were also significant for those 18-49, but in prostate cancer younger age was protective (35% decrease in risk) because younger people, on average, had fewer comorbidities (43.4% of 18-49 had none compared to 31.7% in 50-64, 25.1% in 65-74, and 28.7% in ≥75) . Whereas those aged 65-74 were not significantly different than the reference group, but those ≥ 75 were significantly associated with an increased risk (71%) for HCs.

Patients with colorectal cancer and PP had a 26% increase in risk of having ≥ 1 HC. Unlike breast and prostate cancer, colorectal cancer occurs in both men and women. However, in the analysis men and women did not significantly differ in risk for the outcome. As with prostate cancer, younger age (18-49) was associated with a decreased risk (39%) and older age with increased risk (73%) of HCs. Also differing from breast and prostate cancer patients, chemotherapy was associated with an increased risk of HCs (35%). One explanation for the lowered risk in younger people,

despite an increased risk associated with chemotherapy, could be that younger people had the lowest number of comorbidities (34.1% had none in 18-49 years old) compared to the referent age group (25.5%). Conversely, 75% of those ≥ 75 years had at least 1 comorbid condition.

PP was associated with a 25% increase in risk for the outcome in patients with lung cancer after controlling for sex, age, comorbidity, chemotherapy, and radiation. Men had a 22% higher risk for having ≥ 1 HC than women. Again, since men smoke more and have shorter life spans in general than women, so at the advanced age when being diagnosed with lung cancer we would expect men to have a greater risk for HCs. Both chemotherapy and radiation were significant. We would expect this to be the case since most lung cancers are diagnosed at a late stage.[49] Although surgery may be undertaken in limited scope, treatment often relies on chemotherapy and radiation to eliminate the disease. Having 3 or more comorbid conditions compared to no conditions increased the risk by 69%. Comorbid conditions such as COPD and emphysema are known to occur in people with lung cancer at diagnosis, which would increase the risk of having HCs.

We also noted differences in the association between HC events and type of cancer in the final multivariable LR model. In breast and prostate cancer patients, results showed these cancer types were less likely to have a HC compared to colorectal or lung cancer, and may be explained, in part, by the status of chemotherapy treatment. Being on chemotherapy treatment in both breast and prostate cancers was

not significantly associated with HCs in their respective models (Table 2). In one study, which measured drug-related problems (DRP) (e.g. inappropriate drug, adverse drug reaction) in elderly (mean age 71.1 years) cancer patients, 77.6% were taking ≥ 3 chronic medications concurrently with intravenous chemotherapy and reported to have an average incidence of 3 DRP.[31] Interestingly, adverse drug reactions were reported to be caused by chemotherapeutic agents 85% of the cases; whereas, potential drug-drug interactions were related to chronic use medications 92.6% of the cases.[31] Similar to this analysis, the study on drug-related problems found a statistically significant increase in the odds of having a DRP when taking ≥ 5 medications.[31] However, intensity and duration of chemotherapy were unmeasured confounders in the analysis.

3.6 Limitations

Although efforts were made to address temporality by defining PP in the 1st quarter following incident diagnosis, no assurances can be made that the individual was actively taking the medication preceding the event, or that any combination of medications directly caused the event to occur. Also, although comorbid conditions were controlled for with a summary score, no assessment was made in baseline to assess if the HCs were incident cases, thus allowing for the HCs to be chronic in nature. Further research is warranted that would focus more closely on individual cancers and HCs resulting from concomitant use of medications.

As with any administrative database analysis, the underlying data may lead to misclassification of some individual's cancer or comorbid status. Neither severity nor stage of cancer are included within the database as standalone variables, and hence were not controlled for in the analyses. As such, determination of stage or grade of cancer was not possible. Stage or grade of tumor would be a critical confounding variable, as these would determine the course of action for these patients regarding surgery, chemotherapy, and radiation treatments.

We were unable to conduct any analyses regarding race, as we did not have this variable in the database. Incidence rates for the four most common cancers studied in this manuscript vary by race. For instance, African Americans have higher incidence rates for prostate, colorectal, and lung cancers compared to White, Hispanic, and other racial/ethnic groups.[50]

Intensity of infusion chemotherapy nor strength or dosing of prescription anticancer agents were analyzed for this analysis. The definition used to classify a newly diagnosed cancer patient as PP was based on the number of distinct medication classes and a minimum days' supply during the first quarter following diagnosis. This definition inherently may lead to under- or overestimation of the number of patients with PP because most adherence rates for chronic medications would require reaching 80% adherence. Some definitions of PP have counted individual medications, including counting infusions over their day of activity, which would mean counting them more than once per month to account for administration cycles. Also, we did not account for infusions or injections which may have not been related to anticancer treatment. The focus of defining PP was for outpatient pharmacy filled medications and therefore inpatient drug usage, over-the-counter, and complementary and alternative drugs were not included as potential contributors to PP in this analysis. Although medications were described in this analysis, no formal statistical tests were conducted to assess associations between their concomitant use and HCs. We examined common HCs associated with PP and cancer patients. The study was designed to use medication class because the mechanism of action within drug class would be the same despite different ingredients.

3.7 Conclusions

Newly diagnosed patients with breast, prostate, colorectal, or lung cancer who had PP were all at a higher risk of having ≥ 1 health complication compared to those without PP. When analyzing by type of cancer and controlling for age, sex, comorbidity, chemotherapy and radiation therapy, PP was associated with an increased risk of HCs by over 25% per cancer type. Active chemotherapy treatment was associated with increased risk of HCs in colorectal and lung cancer patients, but not in breast or prostate cancer patients.

3.8 References

1. Prithviraj GK, Koroukian S, Margevicius S, Berger NA, Bagai R, Owusu C (2012) Patient characteristics associated with polypharmacy and inappropriate prescribing of medications among older adults with cancer. J Geriatr Oncol. 2012 Jul 1;3(3):228-237. PubMed PMID: 22712030; PubMed Central PMCID: PMC3375830.

2. Riechelmann RP, Zimmermann C, Chin SN, et al. Potential drug interactions in cancer patients receiving supportive care exclusively. J Pain Symptom Manage. 2008 May;35(5):535-43. doi:10.1016/j.jpainsymman.2007.06.009. Epub 2008 Feb 4. PubMed PMID: 18243638.

3. Masnoon N, Shakib S, Kalisch-Ellett L, et al. What is polypharmacy? A systematic review of definition. BMC Geriatr. 2017 Oct 10;17(1):230. doi: 10.1186/s12877-017-0621-2. Review. PubMed PMID: 29017448; PubMed Central PMCID: PMC5635569.

4. Sarfati D, Koczwara B, Jackson C. The impact of comorbidity on cancer and its treatment. CA Cancer J Clin. 2016 Jul;66(4):337-50. doi: 10.3322/caac.21342. Epub 2016 Feb 17. Review. PubMed PMID: 26891458.

5. Fu MR, Axelrod D, Guth AA, et al. Comorbidities and Quality of Life among Breast Cancer Survivors: A Prospective Study. J Pers Med. 2015 Jun 26;5(3):229-42. doi: 10.3390/jpm5030229. PubMed PMID: 26132751; PubMed Central PMCID: PMC4600145.

6. "Age and Cancer Risk was originally published by the National Cancer Institute." Available Online: https://www.cancer.gov/about-cancer/causes-prevention/risk/age. Accessed April 11, 2019.

7. Karuturi MS, Holmes MH, Lei X, et al. Potentially inappropriate medication use in older patients with breast and colorectcal cancer. Cancer. 2018 Jul 15;124(14):3000-3007. doi: 10.1002/cncr.31403. Epub 2018 Apr 24. PubMed PMID:29689595; PubMed Central PMCID: PMC6033638.

8. Alkan A, Yasar A, Karci E, et al. Severe drug interactions and potentially inappropriate medication usage in elderly cancer patients. Support Cancer Care 2017 Jan;25(1):229-236. Epub 2016 Sep 12. PubMed PMID: 27619388.

9. Reis CM, Dos Santos AG, de Jesus Souza P, Reis AMM. Factors associated with the use of potentially inappropriate medications by older adults with cancer. J Geriatr Oncol. 2017 Jul;8(4):303-307. doi: 10.1016/j.jgo.2017.05.003. Epub 2017 Jun 24. PubMed PMID: 28602709.

10. Riechelmann RP, Moreira F, Smaletz O, Saad ED. Potential for drug interactions in hospitalized cancer patients. Cancer Chemother Pharmacol. 2005 Sep;56(3):286-90. Epub 2005 Feb 25. PubMed PMID: 15731916.

11. Riechelmann RP, Del Giglio A. Drug interactions in oncology: how common are they? Ann Oncol. 2009 Dec;20(12):1907-12. doi: 10.1093/annonc/mdp369. Epub 2009 Aug 27. Review. PubMed PMID: 19713244.

12. Whitman AM, DeGregory KA, Morris AL, Ramsdale EE. A comprehensive look at polypharmacy and medication screening tools for the older cancer patient. Oncologist. 2016 Jun;21(6):723-30. doi: 10.1634/theoncologist.2015-0492. Epub 2016 May 5. Review. PubMed PMID: 27151653; PubMed Central PMCID: PMC4912369.

13. Ussai S, Petelin R, Giordano A, et al. A pilot study on the impact of known drug-drug interactions in cancer patients. J Exp Clin Cancer Res. 2015 Aug 25;34:89. doi: 10.1186/s13046-015-0201-2. PubMed PMID: 26303220; PubMed Central PMCID: PMC4547416.

14. American Cancer Society: Cancer Facts and Figures 2018. Atlanta, Ga: American Cancer Society, 2018. Available online: https://www.cancer.gov/types/common-cancers#1. Last updated February 26, 2018.

15. Nazer LH, Hawari F, Al-Najjar T. Adverse events in critically ill patients with cancer: incidence, characteristics, and outcomes. J Pharm Pract. 2014; Apr;27(2):208–13. doi: 10.1177/0897190013513302. Epub 2013 Dec 6. PubMed PMID: 24319079.

16. Overview: Adverse events. Health.gov. Available online: https://health.gov/hcq/ade.asp. Accessed January 7, 2019.

17. Vohra R, Madhavan S, Sambamoorthi U, et al. Prescription Drug Use and Polypharmacy Among Medicaid-Enrolled Adults with Autism: A Retrospective Cross-Sectional Analysis. Drugs Real World Outcomes. 2016 Dec;3(4):409-425. PubMed PMID: 27873285; PubMed Central PMCID: PMC5127876.

18. Meraya AM, Dwibedi N, Sambamoorthi U. Polypharmacy and Health-Related Quality of Life Among U.S. Adults With Arthritis, Medical Expenditure Panel Survey, 2010–2012. Prev Chronic Dis 2016;13:160092. doi http://dx.doi.org/10.5888/pcd13.160092.

19. Turner JP, Jamsen KM, Shakib S, Singhal N, Prowse R, Bell JS. Polypharmacy cut-points in older people with cancer: how many medications are too many? Support Care Cancer. 2016 Apr;24(4):1831-40. doi: 10.1007/s00520-015-2970-8. Epub 2015 Oct 9. PubMed PMID: 26449548.

20. AHFS Pharmacologic-Therapeutic Classification. 2018 American Society of Health-System Pharmacists. Available Online:

http://www.ahfsdruginformation.com/ahfs-pharmacologic-therapeutic-classification/. Accessed March 5, 2019.

21. Quinn KJ, Shah NH. A dataset quantifying polypharmacy in the United States. Sci Data. 2017 Oct 31;4:170167. doi: 10.1038/sdata.2017.167. PubMed PMID: 29087369; PubMed Central PMCID: PMC5663207.

22. Arondekar B, Curkendall S, Monberg M, et al. Economic burden associated with adverse events in patients with metastatic melanoma. J Manag Care Spec Pharm. 2015 Feb;21(2):158-64. PubMed PMID:25615005.

23. Rassekh SR, Lorenzi M, Lee L, Devji S. Reclassification of ICD-9 Codes into Meaningful Categories for Oncology Survivorship Research. J Cancer Epidemiol. 2010;2010:569517. doi: 10.1155/2010/569517. Epub 2010 Dec 29. PubMed PMID: 21234317; PubMed Central PMCID: PMC3018640.

24. Barber M, Nguyen LS, Wassermann J, Spano JP, Funck-Brentano C, Salem JE. Cardiac arrhythmia considerations of hormone cancer therapies. Cardiovasc Res. 2019 Jan 30. doi: 10.1093/cvr/cvz020. [Epub ahead of print] PubMed PMID:30698686.

25. Tamargo J, Caballero R, Delpón E. Cancer chemotherapy and cardiac arrhythmias: a review. Drug Saf. 2015 Feb;38(2):129-52. doi: 10.1007/s40264-014-0258-4. PubMed PMID: 25577497.

26. Qureshi W, Ali Z, Amjad W, Alirhayim Z, Farooq H, Qadir S, et al. Venous Thromboembolism in Cancer: An Update of Treatment and Prevention in the Era of Newer Anticoagulants. Front Cardiovasc Med. 2016 Jul 28;3:24. doi: 10.3389/fcvm.2016.00024. eCollection 2016. Review. PubMed PMID: 27517038; PubMed Central PMCID: PMC4963402.

27. Lund JL, Sanoff HK, Peacock Hinton S, et al. Potential medication-related problems in older breast, colon, and lung cancer patients in the United States. Cancer Epidemiol Biomarkers Prev. 2018 Jan;27(1):41-49. doi: 10.1158/1055-9965.EPI-17-0523. Epub 2017 Oct 4. PubMed PMID: 28978563; PubMed Central PMCID: PMC5760326.

28. Wildes TM, Dua P, Fowler SA, et al. Systematic review of falls in older adults with cancer. J Geriatr Oncol. 2015 Jan;6(1):70-83. doi: 10.1016/j.jgo.2014.10.003. Epub 2014 Oct 30. Review. PubMed PMID: 25454770; PubMed Central PMCID: PMC4297689.

29. Neuner JM, Shi Y, Kong AL, et al. Fractures in a nationwide population-based cohort of users of breast cancer hormonal therapy. J Cancer Surviv. 2018 Apr;12(2):268-275. doi: 10.1007/s11764-017-0666-4. Epub 2017 Dec 15. PubMed PMID: 29243101.

30. Sattar S, Alibhai SMH, Spoelstra SL, Fazelzad R, Puts MTE. Falls in older adults with cancer: a systematic review of prevalence, injurious falls, and impact on cancer treatment. Support Care Cancer 2016 Oct;24(10):4459-69. doi: 10.1007/s00520-016-3342-8. Epub 2016 Jul 22. Review. PubMed PMID: 27450557.

31. Goh I, Lai O, Chew L. Prevalence and Risk of Polypharmacy Among Elderly Cancer Patients Receiving Chemotherapy in Ambulatory Oncology Setting. Curr Oncol Rep.2018 Mar 26;20(5):38. doi: 10.1007/s11912-018-0686-x. Review. PubMed PMID:29582192.

32. Leiss W1, Méan M, Limacher A, et al. Polypharmacy is associated with an increased risk of bleeding in elderly patients with venous thromboembolism. J Gen Intern Med. 2015 Jan;30(1):17-24. doi: 10.1007/s11606-014-2993-8. Epub 2014 Aug 21. PubMed PMID: 25143224; PubMed Central PMCID: PMC4284255.

33. Dhalwani NN, Fahami R, Sathanapally H, Seidu S, Davies MJ, Khunti K. Association between polypharmacy and falls in older adults: a longitudinal study from England. BMJ Open. 2017 Oct 16;7(10):e016358. doi: 10.1136/bmjopen-2017-016358. PubMed PMID: 29042378; PubMed Central PMCID: PMC5652576.

34. Waters TM, Chandler AM, Mion LC, et al. Use of International Classification of Disease, Ninth Revision, Clinical Modification, codes to identify inpatient fall-related injuries. J Am Geriatr Soc. 2013 Dec;61(12):2186-91. doi: 10.1111/jgs.12539. Epub 2013 Nov 1. PubMed PMID: 24329820; PubMed Central PMCID: PMC3876293.

35. Kim DH, Schneeweiss S. Measuring Frailty Using Claims Data for Pharmacoepidemiologic Studies of Mortality in Older Adults: Evidence and Recommendations. Pharmacoepidemiol Drug Saf. 2014 Sep;23(9):891-901. doi:10.1002/pds.3674. Epub 2014 Jun 24. Review. PubMed PMID: 24962929; PubMed Central PMCID: PMC4149846.

36. Karpov A, Parcero C, Mok CP, et al. Performance of trigger tools in identifying adverse drug events in emergency department patients: a validation study. Br J Clin Pharmacol. 2016 Oct;82(4) :1048-57. doi: 10.1111/bcp.13032. Epub 2016 Jul 8. PubMed PMID: 27279597; PubMed Central PMCID: PMC5137830.

37. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Med Care 1998;36(1):8–27 [Epub 1998/02/07].

38. HCPCS Level II Coding Process & Criteria. Centers for Medicare & Medicaid Services. CMS.gov: A federal government website managed and paid for by the U.S. Centers for Medicare & Medicaid Services. Available online: https://www.cms.gov/Medicare/Coding/MedHCPCSGenInfo/HCPCSCODINGPROCESS.html. Accessed July 30, 2018.

39. Radiation Therapy Services HCPCS Code range G6001-G6017. American Medical Association (AHA). Online: https://coder.aapc.com/hcpcs-codes-range/163/10. Accessed April 8, 2019.

40. Fitch K, Pelizzari PM, Pyenson B. Cost drivers of cancer care: a retrospective analysis of Medicare and commercially insured population claim data 2004-2014. Available Online: http://www.siteneutral.org/2016/04/17/cost-drivers-of-cancer-care-a-retrospective-analysis-of-medicare-and-commercially-insured-population-claim-data-2004-2014-milliman-april-2016/. Accessed April 8, 2019.

41. Kleinbaum DG, Klein M. Logistic Regression: A Self-Learning Text. 3rd Ed. New York: Springer, 2010.

42. Agresti A. An Introduction to Categorical Data Analysis. 2nd ed. Hoboken, NJ: John Wiley & Sons, Inc.; 2007.

43. Murphy CC, Fullington HM, Alvarez CA, et al. Polypharmacy and patterns of prescription medication use among cancer survivors. Cancer. 2018 Jul 1;124(13):2850-2857. doi: 10.1002/cncr.31389. Epub 2018 Apr 12. PubMed PMID: 29645083; PubMed Central PMCID: PMC6147245.

44. Turner JP, Shakib S, Singhal N, et al. Prevalence and factors associated with polypharmacy in older people with cancer. Support Care Cancer. 2014 Jul;22(7):1727-34. doi: 10.1007/s00520-014-2171-x. Epub 2014 Mar 2. Erratum in: Support Care Cancer. 2014 Jul;22(7):1735. PubMed PMID:24584682.

45. Jorgensen TL, Herrstedt J, Friis S, Hallas J. Polypharmacy and drug use in elderly Danish cancer patients during 1996 to 2006. J Geriatr Oncol. 2012 Jan;3(1):33-40. doi:10.1016/j.jgo.2011.09.001.

46. NCCN Clinical Practice in Oncology (NCCN Guidelines): Prostate Cancer, Version 1.2019, March 6, 2019. Available Online. NCCN.org. Accessed April 12, 2019.

47. American Cancer Society. Treatment of Breast Cancer by Stage. Available online: https://www.cancer.org/cancer/breast-cancer/treatment/treatment-of-breast-cancer-by-stage.html. Accessed April 12, 2019.

48. Edwards MJ, Campbell ID, Lawrenson RA, Kuper-Hommel MJ. Influence of comorbidity on chemotherapy use for early breast cancer: systematic review and meta-analysis. Breast Cancer Res Treat. 2017 Aug;165(1):17-39. doi: 10.1007/s10549-017-4295-4. Epub 2017 May 20. Review. PubMed PMID: 28528451.

49. Leduc C, Antoni D, Charloux A, Falcoz PE, Quoix E. Comorbidities in the management of patients with lung cancer. Eur Respir J. 2017 Mar 29;49(3). pii: 1601721. doi: 10.1183/13993003.01721-2016. Print 2017 Mar. Review. PubMed PMID: 28356370.

50. Fast Stats: An interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. https://seer.cancer.gov/faststats. (Accessed on 4-13-2019)

Figure 1. Selection of Patients for Analyses of Health Complications in Adults (≥ 18 years) Newly Diagnosed with Cancer, with or without Polypharmacy, in Optum Clinformatics Data Mart 2011-2014.

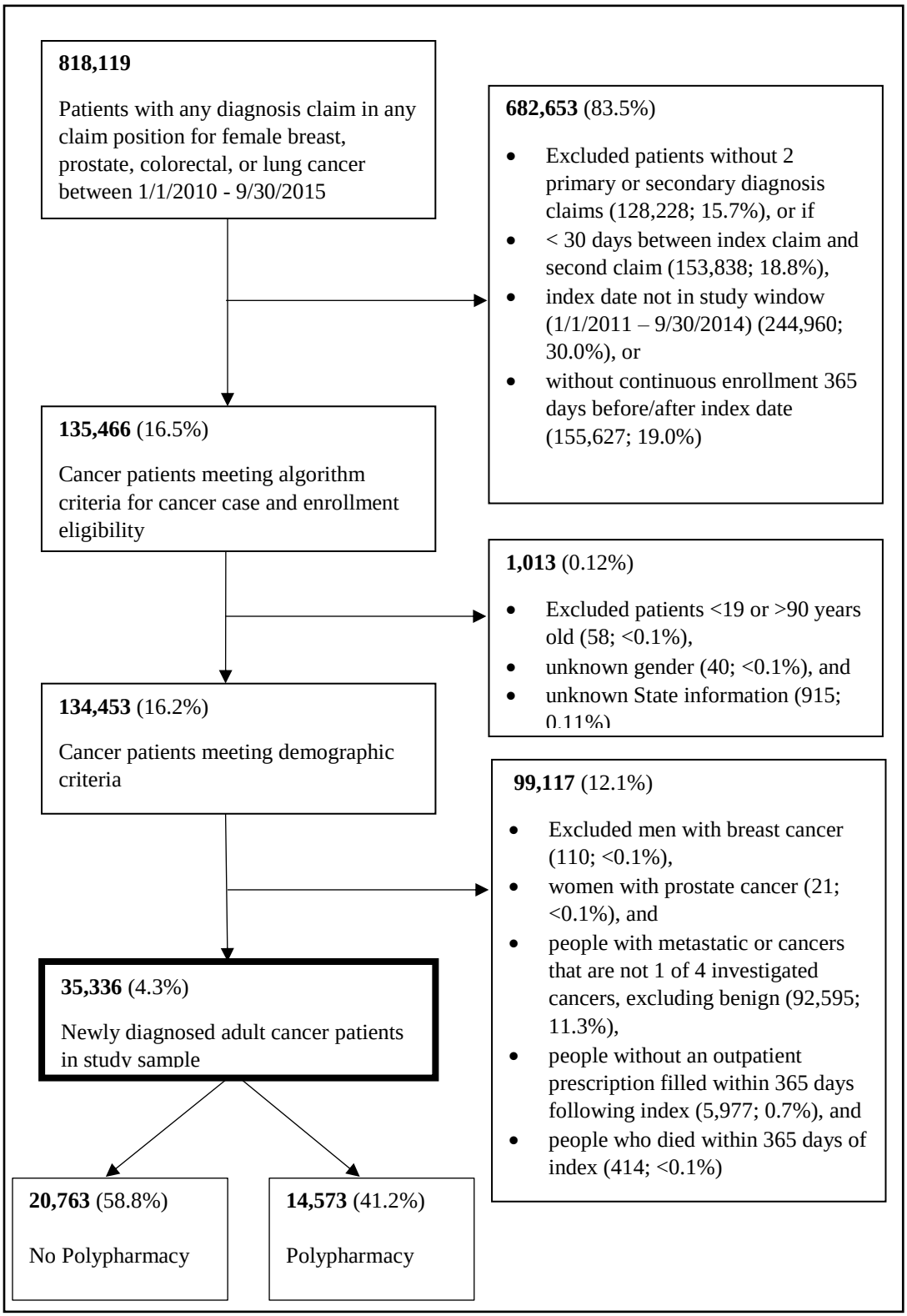


Figure 2. Study Window Timeline (not to scale)

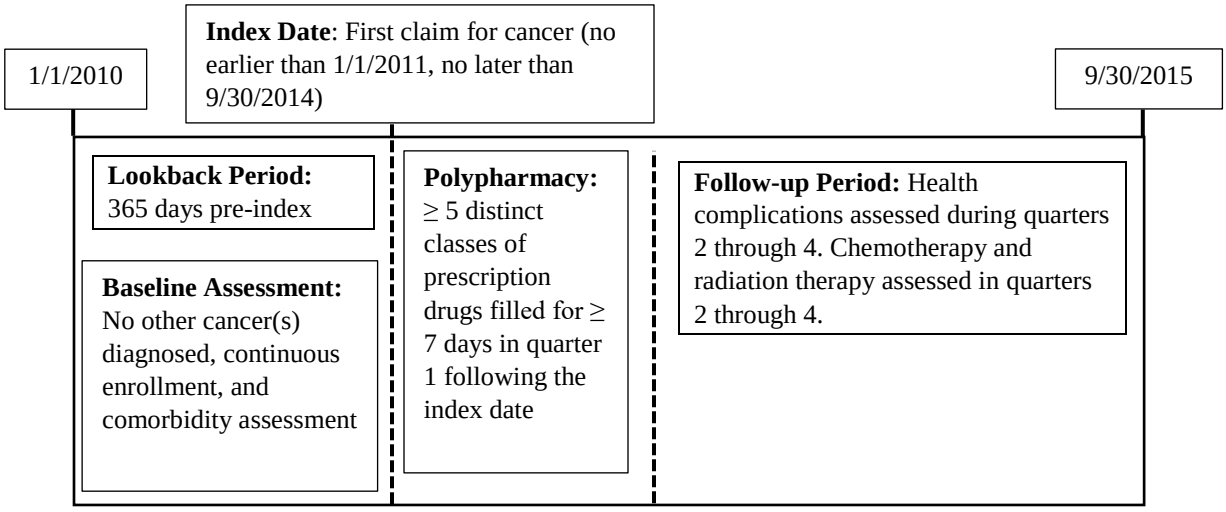


Table 1. Demographic and Clinical Characteristics of Adults (≥ 18 years) with Newly Diagnosed Cancer by Polypharmacy Status During 2011-2015, (N= 35,336).

Demographic and Clinical Characteristics of Cancer Survivors	No Polypharmacy (N= 20,763 | 58.8 %)	Polypharmacy (N= 14,573 | 41.2 %)	p-value
Age group (years)			
18-49	2,014 (9.7)	688 (4.7)	
50-64	7,189 (34.6)	3,618 (24.8)	<.0001
65-74	6,525 (31.4)	5,142 (35.3)	
≥ 75	5,035 (24.3)	5,125 (35.2)	
Sex			
Men	11,164 (53.8)	6,926 (47.5)	<.0001
Women	9,599 (46.2)	7,647 (52.5)	
Region			
Northeast	2,099 (10.1)	1,384 (9.5)	
South	7,531 (36.3)	5,514 (37.8)	<.0001
Midwest	4,287 (20.6)	2,731 (18.7)	
West	6,846 (33.0)	4,944 (34.0)	
Insurance Coverage			
Commercial	10,439 (50.3)	9,775 (67.1)	
Medicare Advantage	10,324 (49.7)	4,798 (32.9)	<.0001
Type of Cancer[a]			
Breast (female)	8,422 (40.6)	6,278 (43.1)	
Prostate	9,898 (47.7)	5,808 (39.9)	
Colorectal	1,854 (8.9)	1,438 (9.9)	
Lung	589 (2.8)	1,049 (7.2)	<.0001
Chemotherapy[b]			
Yes	5,764 (27.8)	5,453 (37.4)	<.0001
Radiation Therapy			
Yes	4,235 (20.4)	2,905 (19.9)	0.2862
Elixhauser Comorbidity Score (baseline)[c]			
0	8,318 (40.1)	2,703 (18.6)	
1-2	9,336 (44.9)	5,721 (39.3)	
≥ 3	3,109 (15.0)	6,149 (42.2)	<.0001
Health Complication (HC)[d]			
Cardiovascular	1,857 (8.9)	2,794 (19.2)	<.0001
CNS and Psychiatric[e]	495 (2.4)	759 (5.2)	<.0001
Gastrointestinal	333 (1.6)	410 (2.8)	<.0001
Hematologic	1,133 (5.5)	1,449 (9.9)	<.0001
Metabolic	236 (1.1)	559 (3.8)	<.0001
Skeletal	725 (3.5)	812 (5.6)	<.0001
Adverse drug-related event	297 (1.4)	430 (3.0)	<.0001
Patients with any HC	3,928 (18.9)	4,963 (34.1)	<.0001

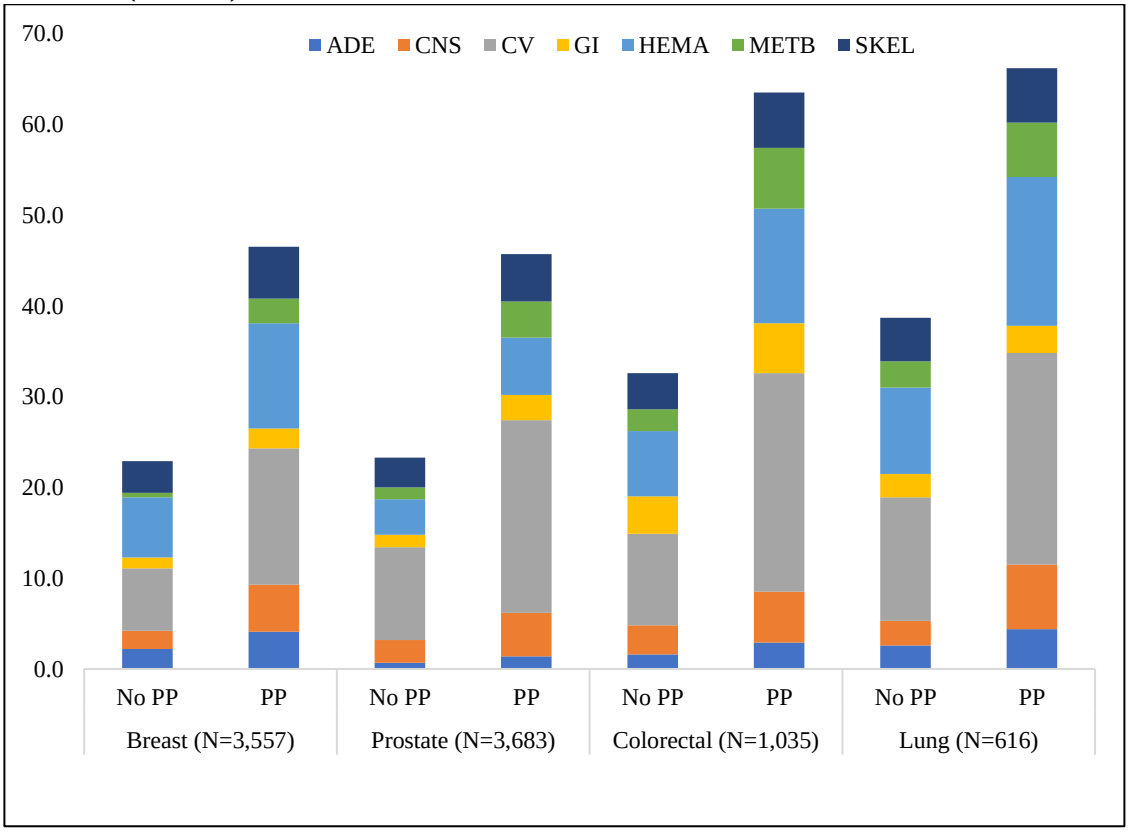
Notes: [a]Codes used to define each type of cancer are in Appendix E.
[b]Chemotherapy was dichotomized into two groups based on absence or presence of at least 1 outpatient prescription claim using American Hospital Formulary System (AHFS) of classification coding or a Healthcare Procedure Coding System Level II (HCPCS) in the range of J8500-J9999 in the follow-up year post-index claim.
[c]Elixhauser Comorbidity Score is the summation of a dichotomized variable for absence or presence of various health conditions found in Appendix F. In this analysis, 4 of the original 31 disease (states) coding groupings were excluded as 3 related to cancer conditions and 1 related to an outcome of interest (arrhythmias). Baseline refers to the time from the index date (first cancer diagnosis) up to 365 days prior to the index date.
[d]Code sets for health complications (HCs) are in Appendix G. HCs were assed in the 2nd, 3rd, and 4th quarter following a patient's incident cancer diagnosis.
[e]CNS= central nervous system.

Table 2. The 20 Most Filled Prescription Medication Classes During the Exposure Window for Cancer Patients, by Polypharmacy, N,% (N=35,336).

No Polypharmacy			Polypharmacy		
Medication Class	**N**	**%**	**Medication Class**	**N**	**%**
HMG-CoA reductase inhibitors	4,492	9.8	HMG-CoA reductase inhibitors	7,816	7.3
Angiotensin-converting enzyme inhibitors	3,047	6.7	Beta-adrenergic blocking agents	5,686	5.3
Beta-adrenergic blocking agents	2,312	5.1	Angiotensin-converting enzyme inhibitors	5,109	4.8
Antineoplastic agents	2,299	5.0	Dihydropyridines	3,617	3.4
Dihydropyridines	1,748	3.8	Proton-pump inhibitors	3,614	3.4
Opiate agonists	1,613	3.5	Opiate agonists	3,508	3.3
Angiotensin ii receptor antagonists	1,483	3.3	Angiotensin ii receptor antagonists	2,754	2.6
Thyroid agents	1,431	3.1	Antineoplastic agents	2,722	2.5
Proton-pump inhibitors	1,346	3.0	Thyroid agents	2,605	2.4
Selective alpha-1-adrenergic block.agent	1,339	2.9	Metformin	2,589	2.4
Quinolones	1,199	2.6	Selective-serotonin reuptake inhibitors	2,468	2.3
Selective-serotonin reuptake inhibitors	954	2.1	Quinolones	1,993	1.9
Other nonsteroidal anti-inflam. agents	937	2.1	Loop diuretics	1,869	1.7
First generation cephalosporins	899	2.0	Benzodiazepines (anxiolytic,sedativ/hyp)	1,847	1.7
Benzodiazepines (anxiolytic,sedativ/hyp)	847	1.9	Selective alpha-1-adrenergic block.agent	1,844	1.7
Thiazide diuretics	808	1.8	Other nonsteroidal anti-inflam. Agents	1,773	1.7
Metformin	645	1.4	Sulfonylureas	1,710	1.6
Corticosteroids (eent)	616	1.4	Anticonvulsants, miscellaneous	1,683	1.6
Aminopenicillins	572	1.3	Thiazide diuretics	1,675	1.6
Anti-inflammatory agents (skin, mucous)	560	1.2	Other diabetes*	1,633	1.5

Notes: Total number of unique prescription classes filled for those without PP and those with PP were 48,116 and 107,619, respectively.
*= drug class name was diabetes mellitus, but to not confuse it with biguanides (metformin) they are listed as Other diabetes.

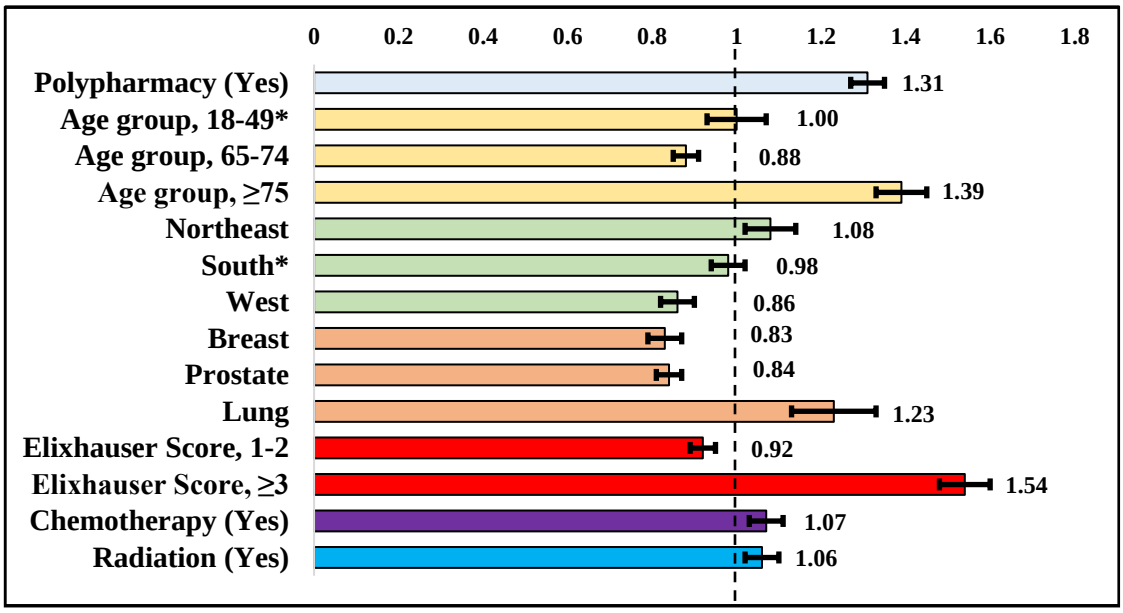
Figure 3. Percentage of Patients with ≥ 1 Health Complication by Polypharmacy and Body System during 2nd, 3rd, and 4th Quarters of the Year Following Incident Cancer Diagnosis for 2011-2015 (N=8,891).



	Breast (N=3,557)		Prostate (N=3,683)		Colorectal (N=1,035)		Lung (N=616)	
HC Group	**No PP (%)**	**PP (%)**	**No PP (%)**	**PP (%)**	**No PP (%)**	**PP (%)**	**No PP (%)**	**PP (%)**
ADE	2.2	4.1	0.7	1.4	1.6	2.9	2.6	4.4
CNS	2.0	5.2	2.5	4.8	3.2	5.6	2.7	7.1
CV	6.9	15.0	10.2	21.2	10.1	24.1	13.6	23.3
GI*	1.2	2.2	1.4	2.8	4.1	5.5	2.6	3.0
HEMA	6.6	11.6	3.9	6.3	7.2	12.6	9.5	16.4
METB	0.5	2.7	1.3	4.0	2.4	6.7	2.9	6.0
SKEL*	3.5	5.7	3.3	5.2	4.0	6.1	4.8	6.0
ANY	18.0	32.5	18.2	32.5	24.1	40.9	28.2	42.9

Notes: HC= health complication; ADE= adverse drug event; CNS= central nervous system and psychiatric; CV= cardiovascular; GI= gastrointestinal; HEMA= hematologic; METB= metabolic; SKEL= skeletal. PP= polypharmacy. *= GI HCs for lung and colorectal differences between PP and no PP were not statistically significant (p-value 0.0556 and 0.7556, respectively), nor for SKEL (p-value 0.3132). All remaining differences between PP and no PP for HC group by cancer type were significant (p-value < 0.05).

Figure 4. Adjusted Odds Ratios (aORs) with 95% Confidence Intervals of Significantly Associated Investigated Variables for ≥ 1 Health Complication, Results of a Multivariable Logistic Regression Model for Newly Diagnosed Adult (≥ 18 years) Cancer Patients in the US 2011-2015 (N=35,336).



Notes: *= not statistically different from reference group.
Reference categories for the investigated variables above were as follows: No polypharmacy, Age group 50-64, Midwest region, prostate cancer, Elixhauser score of 0 (zero), not on radiation therapy (No), and not on chemotherapy (No).
C-statistic for model was 0.66.

Table 3. Multivariable Logistic Regression Results of Adult (≥ 18 years) Patients with Cancer for Odds of having ≥ 1 Health Complication, by Type of Cancer, Adjusted Odds Ratios (aORs) with 95% Confidence Intervals (95% CI).

Investigated Variable	Breast	Prostate	Colorectal	Lung
	aORs (95% CI)	aORs (95% CI)	aORs (95% CI)	aORs (95% CI)
Polypharmacy (ref= No polypharmacy)				
Yes	**1.37 (1.31 - 1.42)**	**1.27 (1.22 - 1.32)**	**1.26 (1.16 - 1.36)**	**1.25 (1.11 - 1.40)**
Sex (ref= Women)				
Men	N/A	N/A	NS	**1.22 (1.10 - 1.36)**
Age group (years), (ref= 50-64)				
18-49	**1.14 (1.04 - 1.25)**	**0.65 (0.51 - 0.83)**	**0.61 (0.49 - 0.75)**	1.66 (0.94 - 2.94)
65-74	**0.81 (0.76 - 0.87)**	1.05 (0.96 - 1.16)	1.03 (0.89 - 1.18)	**0.77 (0.61 - 0.98)**
≥ 75	**1.26 (1.17 - 1.35)**	**1.71 (1.55 - 1.88)**	**1.73 (1.52 - 1.97)**	1.04 (0.82 - 1.31)
Region (ref= Midwest)				
Northeast	1.09 (0.99 - 1.21)	**1.12 (1.02 - 1.23)**	1.00 (0.83 - 1.20)	NS
South	1.05 (0.98 - 1.12)	**0.91 (0.86 - 0.97)**	1.07 (0.94 - 1.21)	NS
West	**0.82 (0.77 - 0.88)**	**0.90 (0.84 - 0.97)**	**0.81 (0.71 - 0.93)**	NS
Elixhauser Comorbidity Score (ref= 0)				
1-2	**0.94 (0.89 - 0.99)**	**0.91 (0.86 - 0.96)**	**0.82 (0.74 - 0.92)**	1.11 (0.95 - 1.31)
≥ 3	**1.40 (1.32 - 1.49)**	**1.70 (1.60 - 1.80)**	**1.54 (1.37 - 1.73)**	**1.69 (1.45 - 1.96)**
Chemotherapy (ref= not on treatment)				
On treatment	NS	NS	**1.35 (1.21 - 1.50)**	**1.33 (1.15 - 1.54)**
Radiation (ref= not on treatment)				
On treatment	**1.10 (1.05 – 1.15)**	NS	NS	**1.25 (1.10 - 1.36)**

Notes: Models were created for each type of cancer with health complications (HCs) as the dependent variable. HCs were dichotomized as absent (0) or present ≥ 1 (1).
aORs in bold font indicate statistical significance where the 95% confidence interval did not cross 1.0 at alpha < 0.05.
NS = not significant during backward elimination modeling. Since each type of cancer was modeled separately, aORs for variables without statistical significance are not shown.
N/A = not applicable to breast and prostate cancer models due to sex-specific inclusions.
Model c-statistics by type of cancer were as follows: breast 0.65; prostate 0.67; colorectal 0.68; lung 0.67.

APPENDIX A

CANCER DIAGNOSES OF INTEREST FOR STUDY POPULATION

Clinical Classification Codes [CCCODEX] of disease medical codes

Diagnosis (type of cancer)	CCCODEX
Cancer of Head and Neck	11
Cancer of esophagus	12
Cancer of stomach	13
Cancer of Colon	14
Cancer of rectum and anus	15
Cancer of liver and intrahepatic bile duct	16
Cancer of pancreas	17
Cancer of Other GI Organs, Peritoneum	18
Cancer of Bronchus, Lung	19
Cancer; other respiratory and intrathoracic	20
Cancer of bone and connective tissue	21
Melanomas of Skin	22
Other Non-Epithelial Cancer of Skin*	23
Cancer of Breast	24
Cancer of Uterus	25
Cancer of other Female Genital Organ	28
Cancer of Prostate	29
Cancer of Testis	30
Cancer of Other Male Genital Organs	31
Cancer of Bladder	32
Cancer of kidney and renal pelvis	33
Cancer of other urinary organs	34
Cancer of brain and nervous system	35
Cancer of thyroid	36
Hodgkin`s disease	37
Non-Hodgkin's Lymphoma	38
Leukemias	39
Multiple myeloma	40
Cancer, Other and Unspecified Primary	41
Secondary malignancies*	42
Malignant Neoplasm Without Specification	43
Neoplasms of Unspecified Nature or Unknown	44
Benign neoplasm of uterus*	46
Other and Unspecified Benign Neoplasm*	47
* = Excluded from analysis; Codes are available at: https://meps.ahrq.gov/data_stats/download_data/pufs/h170/h170app3.html#Top	

APPENDIX B

PRIORITY CONDITIONS AND OTHER CONDITIONS INVESTIGATED

Clinical classification codes [CCCODEX] and International Classification of Disease 9th Edition [ICD-9] medical codes

	Condition	Source	Code
Physical[a]	**Arthritis** (infective & osteomyelitis 201, rheumatoid arthritis 202, osteoarthritis 203, other non-traumatic joint disorders 204)	CCCODEX	201-204
	Chronic Obstructive Pulmonary Disease (COPD) (chronic bronchitis 491, emphysema 492, Bronchiectasis (494), chronic airway obstruction 496), asthma 128,493	CCCODEX	127, 128
		ICD9CODX	491,492, 493, 494,496
	Diabetes (without complications 049, with complications 050)	CCCODEX	049, 050
	Heart conditions (acute myocardial infarction 100, coronary atherosclerosis 101, nonspecific chest pain 102, pulmonary heart disease 103, other heart disease 104, conduction disorders 105, cardiac dysrhythmias 106, cardiac arrest 107, congestive heart failure 108), stroke (hemiplegia 342, cerebrovascular disease 430-438), hypertension (essential 098, with complications and secondary 099)	CCCODEX	096-099
		ICD9CODX	100-108, 342, 430-438
Mental[b]	**Mood Disorder** (depression and bipolar)	ICD9CODX	657
	Anxiety	CCCODEX	651

Notes: [a]Physical chronic conditions were identified using the information provided by MEPS which can be found here: https://meps.ahrq.gov/mepsweb/data_stats/MEPS_topics.jsp. [b]Mental conditions are also from MEPS and can be found here: https://www.hcup-us.ahrq.gov/toolssoftware/ccs/AppendixCMultiDX.txt

APPENDIX C

SETTINGS OF CARE CODES

Medical Expenditures Settings of Care classification codes

Setting of Care	Expenditure Variable
Office-based	OBVEXP[YY]
Hospital Outpatient	OPTEXP[YY]
Emergency Room	ERTEXP[YY]
Inpatient Hospital Stays	IPTEXP[YY]
Prescription Medicines	RXEXP[YY]
Dental	DVTEXP[YY]
Home Health Care	HHHCXP[YY]
Other Medical Expenses	VISEXP[14], OTHEXP[YY]
Note: [YY] represents the placeholder for the 2-digit year associated with the year of the Household Component file. Example OBVEXP14 would be the office-based variable for the year 2014.	

APPENDIX D

PRIORITY CONDITIONS AND OTHER CONDITIONS INVESTIGATED

Clinical classification codes [CCCODEX] and International Classification of Disease 9th Edition [ICD-9] medical codes

Medical Condition	ICD9CODX	CCCODEX
Congestive heart failure	398, 402, 404, 428	108
Valvular disease	093, 394, 395, 396, 397, 424, 746	096
Pulmonary circulation disorder	415, 416, 417	103
Peripheral vascular disorders	440, 441, 442, 443, 444, 447, 449, 557	114
Hypertension, uncomplicated	401, 642	098, 184
Hypertension, complicated	401, 402, 403, 404, 405, 437, 642	099, 183, 184
Paralysis	342, 343, 344, 438, 780	082
Other neurological disorders	330, 331, 332, 333, 334, 335, 338, 340, 341, 345, 347, 649, 768, 780, 784	079, 080, 081
Chronic pulmonary disease	490, 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505, 506	127, 128
Diabetes, uncomplicated	249, 250, 648	049
Diabetes, complicated	249, 250, 648	050
Hypothyroidism	243, 244	048
Renal failure	403, 404, 585, 586	157
Liver disease	070, 456	150, 151
Peptic ulcer disease, excluding bleeding	531, 532, 533, 534	139
HIV/AIDS	042, 043, 044	005
Rheumatoid arthritis	701, 710, 714, 720, 725	202
Coagulation disorders	286, 287, 289, 649	062
Obesity	278, 649, 793	N/A
Weight loss	260, 261, 262, 263, 783	052
Fluid and electrolyte disorders	276	055
Anemia, blood loss*	280, 648	059
Anemia, deficiency*	280, 281, 285	059
Alcohol abuse	291, 303, 305	660
Drug (substance) abuse	292, 304, 305. 648	661
Psychoses	295, 296, 297, 298, 299	659
Depression	300, 301, 309, 311	657

Note: *= must have both ICD9CODX and CCCODEX codes. Due to inclusion/exclusion criteria for the cancer survivor population in the study, the Elixhauser coding for lymphoma, metastatic cancer, and solid tumors without metastasis are excluded as comorbid conditions. MEPS uses 3-digit ICD9CODX and CCCODEX codes. The search algorithm only counted a medical condition as present or absent, and no double-counting occurred if a patient had both the ICD9CODX and CCCODEX codes. If a survivor had both diabetes complicated and uncomplicated, preference was given to complicated. If a survivor had hypertension complicated and uncomplicated, preference was given to complicated.

APPENDIX E

CANCER DIAGNOSES OF INTEREST FOR STUDY POPULATION

International Classification of Diseases, 9th Revision, Clinical Modification Codes

Cancer Type	ICD-9-CM Abbreviated Codes[a]
Breast	174.x, 198.81, 233.0
Colon Rectum	153.x, 197.5, 209.13, 209.14, 209.15, 209.16, 230.3 154.x, 209.17, 230.42
Prostate	185, 233.4
Lung	162.2-162.9, 197.0, 231.2
Note: Codes include carcinoma in situ and metastatic cancer. [a]HCUP CCS. Healthcare Cost and Utilization Project (HCUP). March 2017. Agency for Healthcare Research and Quality, Rockville, MD. www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp.	

APPENDIX F

AGENCY FOR HEALTHCARE RESEARCH AND QUALITY (AHRQ)

International Classification of Disease 9th Edition [ICD-9] medical codes for Elixhauser Comorbidity Score

Medical Condition	**ICD-9-CM Code**[29]
Congestive heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.x
Valvular disease	093.2, 394.x - 397.1, 397.9, 424.x, 746.3 - 746.6, V42.2, V43.3
Pulmonary circulation disorder	416.x, 417.9
Peripheral vascular disorders	440.x, 441.x, 442.x, 443.1 - 443.9, 447.1, 557.1, 557.9, V43.4
Hypertension, uncomplicated	401.1, 401.9, 642.0
Hypertension, complicated	401.0, 402.x - 405.x, 546.1, 642.1, 642.2, 642.7, 642.9
Paralysis	342.x - 344.x, 438.2x - 438.5x
Other neurological disorders	330.x - 331.x. 332.0, 333.4, 333.5, 334.x, 335.x, 340, 341.1-341.9, 345.x, 347.x, 780.3, 784.3
Chronic pulmonary disease	490x-492.x, 493.x, 494x - 505.x, 506.4
Diabetes, uncomplicated	250.0 - 250.3, 648.0
Diabetes, complicated	250.4 - 250.9, 775.1
Hypothyroidism	243 - 244.2, 244.8, 244.9
Renal failure	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, V42.0, V45.1, V56.x
Liver disease	070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 456.0, 456.1, 456.20, 571.0, 571.2-571.9, 572.3, 572.8, V42.7
Peptic ulcer disease, excluding bleeding	531.41, 531.51, 531.61, 531.7, 531.91, 532.41, 532.51, 532.61, 532.7, 532.91, 533.41, 533.51, 533.61, 533.7, 533.91, 534.41, 534.51, 534.61, 534.7, 534.91
HIV/AIDS	042.x-044.x
Rheumatoid arthritis	701.0, 710.x, 714.x, 720.x, 725.x
Coagulation disorders	286.x, 287.1, 287.3-287.5
Obesity	278.0
Weight loss	260.x-263.x, 783.2
Fluid and electrolyte disorders	276.x
Anemia, blood loss*	280.0, 648.2
Anemia, deficiency*	280.1-281.9, 285.2, 285.9
Alcohol abuse	291.0-291.3, 291.5, 291.8, 291.9, 303.x, 305.0
Drug (substance) abuse	292.0, 292.82-292.89, 292.9, 304.x, 305.2-305.9, 648.3
Psychoses	295.x-298.x, 299.1
Depression	300.4, 301.12, 309.0, 309.1, 311
Note: Due to inclusion/exclusion criteria for the cancer patient population in the study, the Elixhauser coding for lymphoma, metastatic cancer, and solid tumors without metastasis are excluded as comorbid conditions. If a patient had both diabetes complicated and uncomplicated, preference was given to complicated. If a patient had hypertension complicated and uncomplicated, preference was given to complicated.	

APPENDIX G

RADIATION THERAPY CODES

Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS)

Description of Procedure	Codes / Code Range	Source[b]
Therapeutic radiology: planning	77261-77263	CPT
Radiation therapy simulation	77280-77299	CPT
Radiation physics services	77300-77370	CPT
Sterotactic radiosurgery	77371-77373	CPT
Radiation treatment	77401-77417	CPT
IMRT delivery[a]	77401-77417	CPT
Steroscopic imaging guidance	77421	CPT
Neutron therapy	77422-77423	CPT
Radiation therapy management	77427-77499	CPT
Proton therapy	77520-77525	CPT
Hyperthermia treatment	77600-77620	CPT
Brachytherapy	77750-77799	CPT
Ultrasound localization of radiation therapy	G6001	HCPCS
Stereoscopic x-ray guidance	G6002	HCPCS
Radiation Treatment delivery	G6003-G6017	HCPCS
Notes: [a]IMRT = intensity modulated radiation therapy. bSources are listed as reference numbers 22 and 23 from manuscript 3.		

APPENDIX H

ADVERSE EVENT CODES

Common Adverse Events and Drug-Related Events in Cancer Patients

Category	Adverse event	ICD-9-CM
Cardiovascular	Conduction disorders; Cardiac arrhythmias; Tachycardia	426.x, 427.x; 785.0
	Secondary hypertension and Hypertension complications; Hypotension	405.x, 458.x
Central nervous system and psychiatric	Seizures/convulsions (not epilepsy); Myoclonus	780.3x; 333.2
	Syncope/collapse/faint	780.2
	Delirium (acute, subacute), Drug psychoses	293.0, 293.1; 292.x
	Neuropathy due to drugs	357.6
Gastrointestinal	Acute gastrointestinal bleeding	[d]531.0x, 531.1x, 531.3x, 532.0x, 532.1x, 532.2x, 533.0x, 533.1x, 533.2x, 534.0x, 534.1x, 534.2x, 535.01, 535.11, 535.21, 535.41, 535.51, 535.61, 535.71, 578.x
Hematologic	Pulmonary embolism or Venous thromboembolism; Anemia; Leukopenia; Neutropenia; Thrombocytopenia;	415.1x, 451.x, 452.x, 453.x; 280.x, 281.x, 285.2, 285.9, 648.2; 288.50, 288.51, 288.59; 288.00, 288.03, 288.09; 287.3, 287.5, 289.84
Metabolic	Acute renal failure	584.x
Skeletal	Fracture	[a]800.xx-829.xx, [a]E880-E887
	Dislocation[f]	[f]830.xx-839.xx
	Intracranial injury[f]	[f]850.xx-854.xx
	Crushing injury[f]	[f]925.xx-929.xx
	Other head injuries (not included in fracture above)	[g]870.xx–873.xx, 900.xx, 910.xx, 918.xx, 920.xx-921.xx, 950.xx-951.xx
	Other spinal injuries (not included in fracture above)	[g] 846.xx-847.xx, 952.xx –954.xx
	Falls	[c]V15.88
Other	Unspecified adverse effect of unspecified drug, medicinal and biological substance	[b]995.0, 995.20, 995.4
	Poisonings by drugs, medicaments, and biological substances; and late effects	[g] 960-977; 909.0, 909.5
	Toxic effects of substances	[g] 980.xx-989.xx
	Adverse effects in therapeutic use of drugs, medicaments, and biologics	[g] E930.xx -E949.xx

Notes: ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification.

a: Ray WA, Griffin MR, Fought RL, Adams ML. Identification of fractures from computerized Medicare files. J Clin Epidemiol. 1992;45(7):703–14. https://doi-org.uri.idm.oclc.org/10.1016/0895-4356(92)90047-Q.

b: Certain health complications not classified elsewhere. ICD9DATA.com http://www.icd9data.com/2015/Volume1/800-999/990-995/995/default.htm

c: Kim DH, Schneeweiss S. Measuring frailty using claims data for pharmacoepidemiologic studies of mortality in older adults: evidence and recommendations. *Pharmacoepidemiology and drug safety*. 2014;23(9):891-901. doi:10.1002/pds.3674.

d: Riechelmann RP, Del Giglio A. Drug interactions in oncology: how common are they? Annals of Oncology 20: 1907–1912, 2009. doi:10.1093/annonc/mdp369.

e: Tamariz et al. A systematic review of validated methods for identifying ventricular arrhythmias using administrative and claims data. *Pharmacoepidemiology and drug safety* 2012; 21(S1): 148–153. Published online in Wiley Online Library (wileyonlinelibrary.com) doi: 10.1002/pds.2340

f: Waters TM, Chandler AM, Mion LC, Daniels MJ, Kessler LA, et al. Use of International Classification of Disease, Ninth Revision, Clinical Modification, codes to identify inpatient fall-related injuries. J Am Geriatr Soc. 2013 Dec;61(12):2186-91. doi: 10.1111/jgs.12539. Epub 2013 Nov 1.

g: Rassekh SR, Lorenzi M, Lee L, Devji S. Reclassification of ICD-9 Codes into meaningful categories for oncology survivorship research. J Cancer Epidemiol. 2010;2010:569517. doi: 10.1155/2010/569517. Epub 2010 Dec 29.